ESSENTIAL PRINCIPLES OF

PATHOLOGY

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CHAPTER 1

INTRODUCTORY

This book is designed primarily for the medical student at the start of his clinical course, when he has satisfied the examiners in his anatomy and physiology, but is not prepared to assimilate a great mass of detailed or theoretical knowledge about diseases which are as yet merely names to him. During the years of his clinical studies, by seeing many ill people, these diseases will gradually take form; when the outlines are grafted to become part of his medical understanding he will be able to search through and read more complete texts without getting confused or bored. This outline, therefore, makes no claim to being exhaustive or a critical review, though it is hoped that most common conditions that the student will meet in his ward work are mentioned in it; it deals with principles rather than details, and with his attitude to pathological studies rather than with providing him with lists of facts.

This has enabled the length of the book to be kept down. It is impossible to learn pathology without access to a good museum and post-mortem room, where the organs can be seen and above all handled; no other way exists of appreciating changes in weight and density and rigidity. An additional economy both in space and money has therefore been achieved by omitting all macroscopic illustrations. This seemed to be the only alternative to the expense and bulk of providing enough to illustrate all points. The inclusion of a considerable number of photomicrographs has, however, been thought worth while, since this method of study of pathological conditions is less easy for the student to grasp.

References are given to more exhaustive studies in which the student can carry on his reading if he wishes. References as support for facts are rarely given. It is hoped that the student will be able to verify for himself that a lot of what is said is true, and moreover the basic principles are rarely discussed in modern papers. This attitude must not be thought to imply that the author is in any doubt about his complete dependence on the work of other people for his facts. The first observer of most common things is hard to discover, and it is doubtful if any value results from a name and a

bracketed date from fifty years ago; at any rate to do this as a routine would merely increase the length of the book. References are in general to monographs rather than original papers; the total bulk has to be kept down, and original papers are on the whole too numerous, scattered, fragmentary and often inaccessible to be a profitable field of inquiry for the student with limited time at his disposal. Individuals who wish to follow up further will find references in the monographs.

Pathology as a Study

Pathology means most to those who regard it not as an end in itself or a complete examination subject but as a bridge between the basic sciences of anatomy and physiology and the clinical practice of medicine and surgery. This book tackles the subject not from the angle of those who are going to devote their lives to pathological research, who will in any case require a fuller and larger volume with more detail and discussion, but from the point of view of those who wish to practise medicine in any branch more easily and successfully because they understand the principles underlying human disease.

Although pathology is sometimes defined as the scientific study of disease, this is too wide a definition; it is to be hoped that the student will pursue his clinical studies and ultimately his medical practice with a scientific and inquiring attitude. Pathology endeavours to simplify this scientific study of disease by excluding certain distractions and then breaking up the complex of disease into its components—a form of process analysis of disease. The clinician has to take many other things into account; the patient is a being whose social and mental background, endurance of pain, willingness to submit to prolonged or uncomfortable measures must all be matters of first importance; he may have suffered previous illness, latent or active now, which will radically change your attitude to the problem for which he has actually consulted you; he is likely to exhibit a number of diseases simultaneously, though one may be more important. Even when the disease in question is apparently isolated and named, many different things make up the pattern. For example, in subacute bacterial endocarditis, the patient has an active bacterial focus in his body; his heart valves bear easily detached fragments of clot which may be carried to different parts of his arterial tree with different results in his symptoms; the disturbance of his heart action leads to unusual heart sounds and to an impairment of cardiac function. Again, a patient in the late stages of Bright's disease in uraemia may have symptoms due to renal failure, symptoms

due to heart failure, symptoms due to hypertension, possibly symptoms due to his treatment; in pathological studies we attempt to separate these things and study them independently. For a time then in his pathology the doctor lays aside those feelings which make medicine a humanity and an art rather than a science, and accepting that the patient will always present a mixture of processes and that a disease usually does so, he attempts to analyse these processes into their simplest components in the hope that from this study understanding of these processes will emerge, so that he can assist or interfere with them as is indicated. In pathology we are concerned with the natural mechanisms of recovery and repair as well as with the study of the causes of disease.

The Human Body

The human body is an organism conceived and built up by cellular activity from one cell, which contains the chromatin that is to be distributed to all the different cells of the body to enable them to carry out their functions. It is difficult to avoid the concept that at about the age of 21 a mature state is reached, which thereafter awaits (and repels with varying success) certain processes of ageing and decay; all this interrupted at various times by onslaughts from competitive living organisms. For the pathologist this is a dangerous conception, since it obscures the fact that throughout the whole existence of this colony of cells they, and the extra-cellular material they accumulate, undergo a continuous exchange of material with their environment. In some places the continuous cellular growth is obvious, e.g. hair, skin and nails; in bone it can be demonstrated by staining the bone laid down at any period with madder, as was done by John Hunter (1760), and observing the alterations in the staining as the animals grew older. In a few instances, e.g. nerve cells, and perhaps some others, cellular growth does not appear to occur; but isotope studies have shown that here too there is continuous exchange on the molecular level both in the nucleoprotein and in the cytoplasm and its derivatives, the rate of exchange, admittedly, being not as rapid as in the plasma proteins or red cells, but more rapid than in the most inert tissues such as the structural collagen.

To the conception then of the body as a continuously alive and functional colony of cells we must add that even the apparently permanent materials, both extra- and intra-cellular, are undergoing continuous change; the terminal changes of ageing and decay are special cases of replacement of material which is satisfactorily replaced in health.

The Causes of Disease

This colony of cells does, however, arise from a single fertilized cell, which contributes to it the entire store of chromatin on which growth and differentiation are based. The miracle, by which the minute microscopical but ordered chain of nucleoprotein molecules first builds copies of itself, and then gradually distributes parts of its duties to groups of its offspring, is being slowly worked out by embryological studies; it is astonishing how rarely this process goes wrong in spite of its complexity. It can be seen, however, that disease may arise either (*a*) from faulty original chromatin and that faults here cannot be put right in development; or (*b*) from abnormalities in the development of the embryo; these two causes of disease are frequently referred to as *congenital.* The whole process often goes on in the obscurity of the uterus, though there are many congenital abnormalities which do not show up till later: the best example of this is the (rare) Huntington's chorea, a nervous disease of which the genetic basis is well known but which does not produce symptoms till late adult life. For our purpose it will be necessary to split the term " congenital " into—

1. Genetic: inheritance of faulty chromatin; the fault occurs before fertilization.

2. Developmental: environmental abnormalities in the uterus which result in the faulty formation of the embryo. The distinction should be made where possible, but since it is impossible to alter the uterine environment of the human embryo and difficult to transplant animal embryos, it may not be possible to prove that the whole fault lay in the uterine environment and none on the original chromatin.

The precise time at which cellular multiplication ceases in different organs varies greatly, some, e.g. neurones, cease to divide quite early in intra-uterine life, some, e.g. the kidney, in the first year after birth; some of the epiphyseal cartilages cease growth and are gradually destroyed by ossification during each year in the teens and early twenties—*epiphyseal union.* During all this growth phase, the cell multiplication has exceeded cell loss; there does not come a single moment at which the order to stop growth is given, and thereafter all is cellular destruction, but the rate of multiplication drops gradually and evenly in the later years of growth until when adult life is reached, multiplication is more or less equal to loss. It is only after a further period of years that a further gradual decline takes place so that tissue is lost by *senile atrophy*; and even

in all this change, as much is gain or loss of intra-cellular or extra-cellular substances as of actual cells.

Our evidence on growth in internal organs is largely dependent on observation of mitosis in the cells. This is not wholly reliable; alteration in the speed of mitosis will alter the number seen in a section; there are always fewer in human material obtained at post-mortem than in material removed at surgical operations; some cells can probably multiply without mitosis.

It may make a great difference to the effect on a cell whether it is hit by some injurious agent during an active growth phase, or while inert; the same cause may thus have two different effects, and in considering the cause of disease it must be remembered that the state of the tissue acted on may be more important to the result than the actual damaging agent.

Although the rapidity of growth is most conspicuous in youth, the amount of cellular and chemical exchange taking place in the whole of adult life is probably greater in total. If one takes arbitrarily twenty years for growth followed by forty years of adult maintenance of tissue, it will be seen that slight effects going on for a long time may be of greater importance in adult disease than is usually allowed.

During the whole of this part of life, as well as in the uterus, nutrition is required. A very important source of disease will arise, therefore, from—

3. Deficiencies of essential substances—in quantity or quality—including the common oxygen, water, fat, protein, carbohydrate, as well as common mineral elements, and a highly important group of substances of which only traces are required.

4. Poisoning will occur if substances are present in excess of those which the body can dispose of—again, some normal substances only if in large excess: oxygen, water, salt; some in the merest traces: cyanide, strychnine.

5. As soon as the baby is born it has to compete with a hostile external environment, including both non-living agents (heat, cold, radiations) and living agents of all sizes. Mechanical injury (trauma) and loss of blood and the forms of inflammation are the result. These make up the largest part of human disease even to this day; in more primitive societies, and up till the last hundred years in civilized countries, they were the outstanding cause of disease. Man rarely lived long enough to develop malignant growths and severe degenerative diseases; the mortality of new-born children and a high death-rate from infectious disease in childhood and youth meant

that of ten or more children two survived to continue the species. The same is true of animal wild populations at the present day; apart from ill-understood wider fluctuations, sometimes due to climatic causes or the activities of man, animals reproduce actively, but of all their progeny two survive the hazards of predaceous animals and infection to reproduce in their turn; the moment they lose the sharpness of their senses or the power of their muscles from age they are eaten.

Defences against Micro-organisms in the Environment

Shortly after birth exposure to the world leads to the acquisition of bacteria which thereafter are constantly present in and around the body in the following categories—

Tolerated commensals living on the unwanted by-products of the skin and internal passages.

Actually beneficial organisms, either synthesizing essential material, e.g. vitamin K in the colon, or in the lower animals assisting digestion (several examples), or else useful in that their presence inhibits the growth of the third group.

Pathogenic organisms associated with disease.

They are classified in this order because that is the order of their frequency, and to counteract the old idea that all germs were harmful and a perfectly sterile system was desirable. In the past, this idea mattered little because it was unattainable, although it led to some unnecessary surgical procedures; now the attainment of sterility is at least temporarily possible with the use of powerful drugs (sulphonamides, antibiotics) one of the principal hazards of using these drugs has turned out to be the destruction of harmless commensals or beneficial organisms, which has freed a niche for colonization by much less desirable organisms, many pathogenic, previously of little account in pathology because in the presence of a normal flora they were never able to establish themselves.

The defence of the surfaces of the body against pathogens is therefore partly maintained by the surfaces themselves, partly by the presence of the normal flora. The discussion of the latter method belongs to the companion volume on bacteriology and will not be repeated here. Surfaces exposed to the environment are—

1. Skin, covered by keratinized squamous epithelium and equipped with hair follicles, sweat and sebaceous glands.
2. Internal passages lined by non-keratinizing squamous epithelium, without hairs, sweat or sebaceous glands, but sometimes with

mucous glands: the mouth, oesophagus, vulva and vagina, glans penis.

3. The respiratory tract, lined by ciliated columnar-celled mucus-secreting epithelium.

4. The alimentary tract, lined by mucus-secreting epithelia differing slightly from place to place, and equipped with enzyme-secreting glands discharging on their surface.

The basic methods of defence available in these situations are (*a*) growth mechanically displacing the organisms; (*b*) ciliary action; (*c*) mucus secretion washing them away; (*d*) enzyme and other action rendering the situation impossible for bacterial growth.

1. Skin Surfaces

The nature of the keratin, i.e. hard dry scleroprotein, is in itself a rebuff to all except a few specialized organisms. Certain fungi can establish themselves in moist keratin, but dry skin (with a visible growth rate casting off organisms faster than they can multiply) is all but immune to invasion. The appendages are the weak point. The hair follicles and sebaceous glands are fatty, and provide mechanically satisfactory corners for growth, and the secretion of the sweat glands gives opportunities. Continually damp skin is almost impossible to maintain sterile even with antiseptics in the face of continual airborne organisms. The same is true of surfaces where there is a breach which allows discharge of serum on the skin, e.g. the eczemas, even where the cells are still present and growing. Breaches of the surface, wounds or burns or ulcers, are important in proportion to their extent, for in the absence of the epithelium the second line of defence is needed (inflammation). In general, however, intact squamous keratinized epithelium is so good a defence that destruction of it (ulceration) is almost never the direct result of bacterial attack from the surface. An infected ulcer in this site means either secondary infection of some other primary disease of the epidermis, or is due to attack by bacteria from below.

2. Non-keratinized Mucosae of Mouth, Vagina, Oesophagus

Although these are apparently more delicate, being moist, mucus-covered and without keratin, they are almost as immune to surface bacterial attack. This is partly the effect of growth, of the flow and movement of the mucus over them and of the passage contents, but also the effect of the normal non-pathogenic flora. In consequence this balance is more nicely poised, and slight alterations due to debility of the patient, absence of leucocytes, antibiotic upset

of bacterial balance, will lead to ulceration, often caused by organisms normally present in the cavity in a suppressed state (Vincent's angina, Cancrum oris, the pharyngeal ulceration of agranulocytosis). The normal flora may be dependent on the physiological state of the mucosa; the immature vagina of the young girl is much more easily colonized by the gonococcus, and this organism can be most satisfactorily expelled by the action of oestrin on the epithelium; similarly the normal acid-producing flora of the adult vagina is hostile to the invasion of the Trichomonas.

3. Ciliated Columnar Epithelium

Particulate material of any sort found on a ciliated surface is trapped in the mucus and beaten along the surface by the cilia, finally to be ejected from the respiratory tract by a cough or a sneeze. This applies to living as well as dead material, but the mechanisms are delicate, easily upset by irritants, and easily saturated. Although lifting mucoid material easily, the cells are less successful with fibrinous, purulent or other thick fluids, and they are poisoned by the toxins of pus. Further, they are depressed by common vapours, the volatile anaesthetics being a particularly important example.

4. The Alimentary Tract

On the one hand, this has to deal with the regular introduction of micro-organisms of all sorts in the food and drink; on the other there is a continuous discharge of the contents. In spite of this continuous change, the bacterial inhabitants of the gut are curiously static, the occasional pathogenic intruder rarely establishing itself.

The first defence is the acidity of the stomach. This is low in infancy, and bacterial infection of the gut, therefore, begins soon after birth. In many lower orders of life, this colonization of the gut is essential for digestion the cellulose of plants is digested in the herbivora by bacteria and protozoa, and wood-eating insects are similarly dependent on bacteria or fungi. In man though the colonic bacteria are important synthesizers of vitamins no digestive function is known. A small number of organisms of no pathogenic importance maintain themselves in the stomach in spite of the acidity, but both the stomach and the small gut are effectively sterile.

The acidity may be dodged because of (*a*) poor mixing of large masses of food; (*b*) rapid transit, particularly of organisms in water which is passed at once into the duodenum: water-borne pathogens are therefore peculiarly dangerous; (*c*) at least theoretically achlorhydria may permit the access of organisms to the gut, though no

particular inflammation is known to be more common in those with achlorhydria. For these reasons *in vitro* studies of bacterial growth in gastric juice are incomplete evidence.

Persistent peristaltic movement, secretion of mucus and the rapid rate of growth of the mucosal cells—if we judge by animal experiment, the mucosa of the intestine renews itself daily—these three factors dispose of most abnormal bacteria in the colon; the exaggeration of these is the diarrhoea by which intestinal irritants are removed. The vast number of tolerated commensal organisms in the faeces utilize foodstuff that would be available for pathogens, and as long as they stay in the colon they are harmless if not useful. Out of place, however, these organisms are pathogenic, e.g. the pyelitis of the kidney caused by *Bacillus coli*.

In all these surfaces there is a natural physiological balanced state which controls bacterial growth without much expenditure of energy by the body. When these physiological lines of defence fail, the second line of defence, *inflammation*, begins; it is conventional to regard this reaction as belonging to the science of pathology though there is no sharp distinction between the normal or physiological and the pathological here, except one of convenience in breaking up a large subject.

6. From the start the colony of cells has to maintain its integration; since surface nutrition is impossible for multicellular organisms a transport system must be developed, and the blood-system develops in the embryo about the fourth week of life, with effective cardiac action from about the eighth week. As soon as the outer world is reached the respiratory and alimentary functions are separated and transferred from a foetal organ, the placenta, to the systems by which respiration and nutrition are carried out in adults. There are thus groups of diseases due to—

Failure to Maintain Mechanical Transport in the Body

The system most affected is the blood, but all passages are included. The causes of the failure are most often changes which are largely described as *degenerative*, a term which does not clarify the causes and results very much, but degenerative arterial disease leading to impairment of blood supply is in total one of the major causes of disease in those past middle life.

7. The interest that our grandparents showed in the conquest of inflammations has been rewarded in civilized present-day

communities, and we in our turn are surviving long enough to be able to be worried about illnesses which broadly speaking take place in the post-reproductive life. The particular problem at the moment is that of malignant disease or cancer: a *disorder of growth* which is of little biological importance in that it occurs principally at ages when the bulk of life's work is done and reproduction over. It is therefore a tendency which has no genetic disadvantage; as far as we know, those who are going to develop it are not handicapped in the struggle for existence as they would be if the condition were fatal before reproduction, and the disease does not breed itself out as complete non-resistance to common pathogenic organisms might.

These causes of disease described above are equally valid when applied to the body as a whole, or to the individual organs of the body in what is sometimes described as the *special pathology* of organs, in which local modifying factors are present. They result in what is known as organic disease, because structural and chemical changes can be objectively demonstrated. The powers of reason and memory in the human mind which give man his advantage over the animals may become disordered in themselves, quite apart from the effects of structural and chemical changes in the body. Some disorders of the mind are quite clearly related to primary abnormalities in chemical processes and research may add to their number, but it is likely in others that the start of the trouble is in the processes of reason and in the adjustment of the man's mind to the world around him, to society and responsibility, and to the certainty of death; the whole physical and chemical mechanism of his body is secondarily affected.

This mental disease is at least as important numerically as any other, but for many reasons cannot be included in this book. Little of the basic study of normal psychology is available to build on, whereas physiology and anatomy have been studied; there is great confusion and scanty agreement among the experts, whose terminology is involved and whose arguments are often not easy to follow. But in leaving the pathology of mental disease to post-graduate study we must be continuously on the look-out in our studies of organic disease for interactions between body and mind.

These then are the main causes of disease at the present day. It is more convenient to alter the order for discussion to bring to the front the simpler conceptions, and those which are already a matter of day-to-day experience for anyone who has survived in this world long enough to be a student, i.e. the effects of injury and inflammation. Those diseases which are more intricate or less frequently observed will be discussed later. We have therefore—

1. Inflammatory Responses

The remainder of the body is healthy; this is a local reaction to local conditions by a physiologically efficient organism. The causes divide into: (*a*) non-living agents; (*b*) living agents: bacteria, viruses, protozoa and metazoan parasites.

2. Mechanical Breakdown in Transport

Again it is assumed in the first place that the remainder of the body is healthy.

3. General Conditions due to Deficiencies or Excesses of Particular Substances

Often predominantly affect one organ or tissue, but may be widespread in their effects—

(*a*) *Extrinsic*: oxygen; dietary deficiencies; vitamins and trace elements. Excesses of normal substances; poisons of known structure; toxins.

(*b*) *Intrinsic*: endocrine excesses and deficiencies.

4. Disorders of Growth—Benign and Malignant Neoplasms

5. Disorders of Reproduction

Genetic; developmental: effects of foetus on mother, and effects of mother on foetus.

The table of contents will show how these sections are broken up into smaller parts; it should be realized that the sections are not of equal importance.

REFERENCES

Throughout his study the student is advised to refer to longer volumes whenever a subject particularly interests him, or when he sees a clinical example. The author acknowledges his own very deep indebtedness to the following books for the aid and inspiration they have given him in his own study of pathology quite apart from the help in writing this book—

PAYLING WRIGHT, G., *An Introduction to Pathology* 3rd Ed. (London, New York and Toronto, Longmans, 1958).

A very full and valuable account both of the historical approach to pathology and of present-day ideas; much more than a mere introduction.

ANDERSON, W. A. D. (Ed.), *Pathology*, 3rd ed. (St. Louis, Mosby, 1957).

The only up-to-date large reference book on the whole subject with lists of original papers. Too bulky for routine reading, but ideal to turn up what is known about uncommon conditions.

HADFIELD, G. (Ed.), *Recent Advances in Pathology* (London, Churchill). Both the most recent edition (1953) and the previous (1947) edition have valuable articles on many important aspects of present-day research.

Hadfield and Payling Wright should be read by all students, in the course of their studies before the qualifying exams.

WHITE, R. G., *Essential Principles of Bacteriology* (London, Pitman Medical Publishing Co. Ltd.). A companion volume. (Ready 1960. Referred to in the text simply as " Bacteriology.")

CHAPTER 2

THE SOURCES OF PATHOLOGICAL INFORMATION

IN the study of disease whether in man or animals four main sources of information are available. There is the observation of the course and incidence of the disease in the patients, i.e. *clinical observation*; the examination of material obtained from his body by cytological, chemical and bacteriological methods, particularly applied to the accessible blood and urine, i.e. *clinical pathology*; the examination of the changes in his tissues, whether obtained by surgical operation (*biopsy*) or after death (*necropsy or autopsy*); and the study in experimental animals of hypotheses based on the above about the cause of the illness. The value of these sources varies and the weight attached to the information varies accordingly, but they form suitable heads under which to consider what is known about any disease.

It should be noted that the collection of information for making a clinical diagnosis of a condition is one thing, the collection of facts in the study of a disease much more laborious. A single examination of the patient's blood may be all that is required to establish a diagnosis with no other facts at all, clinical or otherwise; but no advance in the knowledge of the disease can be expected from such isolated observations. The more the four sources are given a chance to illuminate each other the more valuable do they each become.

1. Clinical

The patient's story may be inaccurate and unreliable but in human medicine it is usual to begin with it, and, apart from human advantages gained when treating a patient, it is the correct procedure. No other source of information is available for the duration of the disease, even its approximate duration, or for the course of events before the patient came under scientific observation. The occupation and other contacts with unusual substances or animals may be of vital importance. The timing and character of onset may help; family incidence suggests a possible genetic background, and contact with similar cases an infectious cause.

Never, therefore, should any pathological inquiry be started without as much clinical information as possible; separation of clinician and pathologist is detrimental to both.

2. Clinico-pathological

Since, in general, chemical changes precede visible cellular changes, and since information is gained more easily for the patient by examination of fluids obtained by puncture than by operation, this source of information should be considered next. Urine examination is simple and the obtaining of blood by venepuncture little more harsh for the patient; cerebro-spinal fluid may be obtained with slightly more trouble, and effusions into cavities may be similarly aspirated.

After the colour, quantity and pressure of the fluid have been noted, it may then be divided up for examination by the bacteriologist for the presence of micro-organisms which may or may not be the cause of the illness and indeed may be merely contaminants; the cytologist who will determine the types and numbers of the cells present; and the chemist to estimate the amounts of normal constituents and the presence of abnormal substances.

All have their difficulties: the intermittent changes in the body may mean that bacteria for example are absent in the single sample; this can be overcome up to a point by repeating the observation, but there is a limit to the total amount of investigation available for any patient, and a bacterial invasion of the blood that occurs once in a day for half an hour may well be missed. This is the first point; these examinations relate to a single point of time in material in which the values may fluctuate widely and rapidly.

Bacteria found may be contaminants; the conditions of collection of the sample must be known, to exclude this. Only constant watchfulness will prevent the diagnosis of contaminants as serious organisms. Even when the organisms are derived from the patient, many are normal inhabitants and secondary invaders. Too much must not be read, therefore, from the presence of organisms in any fluid. Conversely there is no guarantee that organisms present will be discovered. The media on which the attempt is made to grow them are limited in number; many organisms are highly delicate and critical conditions may be necessary for their growth; some indeed have never been grown at all, and the group known as the filter-passing viruses are too small to be seen with the light microscope.

Even when the organism is obliging enough to grow in the unnatural conditions of the bacteriologist's media there is no proof that its metabolism or toxin-excretion is the same as when it is in

the body. Examples of exotoxins produced both *in vivo* and *in vitro* are well known (diphtheria and tetanus) but many other organisms (tuberculosis) produce effects on cells of the body by mechanisms the chemistry of which is still obscure.

Before bacteria extracted from a lesion are accepted as the cause of it, three conditions must be satisfied: (*a*) the organism must be present in every example of the condition at least at some stage of the process; (*b*) it must be grown in pure culture and after being freed this way from contaminants must (*c*) reproduce the disease on inoculation into an experimental animal.

A fourth condition added by some workers is that antibodies to the organism should be demonstrable (see Bacteriology, for details).

These conditions, referred to as *Koch's postulates* after the great German bacteriologist who first laid them down, are more often than not only incompletely satisfied. Many organisms are hard to grow, some exceptionally so; a good example is the organism responsible for leprosy, which is present in enormous numbers in the tissues of most cases of leprosy, but has not yet been satisfactorily grown in pure culture. Many are hard to demonstrate, because they occur only for a short time in the lesion, are minute or even invisible or do not readily take up the chemical stains used to demonstrate them. There is a considerable species variation in the capacity of an organism to produce disease: some, like the virus of infective hepatitis, will do so only in the human.

Although, therefore, it may not be possible to satisfy Koch's postulates entirely, an attempt should be made, when thinking about the causation of the disease, to proceed along these lines; if they are satisfied, it is very difficult to believe that the organism is not causally related. It should, however, be emphasized that disease in the sense of illness implies, in addition to the organism, a susceptible patient; many people undergo infection, with minimal symptoms, develop immunity from such, and give shelter to the bacteria which fulfil Koch's postulates without actually showing illness; this is called the *carrier state* and is very important in the epidemiology of disease. The full implications of this are discussed in the Bacteriology volume.

Many of the same difficulties beset the chemical and cytological examination of fluids. The sample can be obtained a limited number of times, perhaps once or twice for those which can only be obtained with some discomfort to the patient, twenty or more for others, and intermittent or rapidly fluctuating changes may be missed.

CYTOLOGY apart from haematology is only beginning to come into its own. The examination of individual cells is hampered by

the difficulty of distinguishing them accurately; the easily sorted red and white blood cells have been thoroughly studied for fifty years or more. Differentiation of large mononuclear cells in the fluids from pleura or peritoneum or cerebro-spinal spaces has been less satisfactory. In the last decade, following the lead of the American pathologist Papanicolaou, cells desquamated from many internal surfaces have been studied with particular reference to the identification of the cells of malignant growths; this is a well-tried method of making the diagnosis in cases of carcinoma of the lung or the female genital tract. Its use for other purposes has hardly begun.

CHEMICAL ANALYSIS has been immensely simplified by the advent of chromatographic methods and flame photometry, so that investigations not known ten years ago are now commonplace; micro methods have enabled many observations to be made on the limited volumes of fluid that can be taken from the living patient, and the microgramme quantities of many important physiological substances can be accurately estimated. As a result the investigation of the patient and his disease can be completed before structural changes have gone very far; the new pathology is based on chemical changes rather than on descriptive structural material, and this biochemical pathology of the living is going to increase in importance. With the increased depth of our understanding comes an increased complexity of the chemistry in our picture of disease, but diagnoses are made earlier and control in treatment is much more effective.

The methods of bacteriology, cytology and chemical pathology are usually combined under the heading of *clinical pathology*, as distinct from the study of dead preserved tissues of the body which is referred to as *morbid anatomy*.

3. Morbid Anatomy

The visual study of the changes in the organs of the body in disease is a very old study that is thought at the present to have lost some of its value. It is faced with its own difficulties just as the other methods of study are, and it has suffered from the relative ease with which appearances can be seen and recorded; this leads to a superficial attitude with impressions rather than facts, often buttressed by an authoritarian attitude by the senior pathologists. For many years the only form of pathological study, it first had to link up with bacteriology and now with chemical study. It should always be combined with these studies, and not regarded as competing with them; its scope is by no means finished although the simple descriptive morbid anatomy of the past is now nearly complete. The student should be particularly careful not to use morbid anatomy

as a synonym for pathology; many still believe the pathology of a disease consists of a recital of the later visible changes of disease, macroscopic or microscopic.

Two levels of visual study are possible—naked-eye, and microscopic. It must be accepted that the cellular changes in disease will depend on chemical changes, and that every morphological appearance is but the gross extension of invisible alterations in the material of which the cells are composed; morphological changes will therefore be late, and naked-eye changes will be later still; and by the time these changes are visible the primary cause of the disease may no longer remain pure and isolated, but be overlaid with secondary changes, e.g. the broncho-pneumonia that terminates a coma due to some chemical poison that produces no visible (even microscopical) changes of its own.

NAKED-EYE STUDY has two great advantages: it requires little equipment and is rapid; and thorough survey of large organs and of the body as a whole cannot be carried out by any other method. These are to be set against the disadvantage of the advanced state of the disease when tissue changes become visible. It will hold these advantages only if experience is gained by checking with all other sources of information, and in particular with microscopical study. Without a preceding note of the gross changes, the microscopic examination of a small field loses its value; the two techniques, and the chemical alterations at the back of both, should be constantly linked in your mind.

The correlation of clinical signs and symptoms with gross alterations in the tissues has its foundations in the work of Morgagni in 1761; it still remains a part of medical education to take what chances are available to check your findings in the living body with what is going on in detail inside that body; even if the research into the causes of disease is no longer dependent on morbid anatomy, there is much to be learnt from techniques whose simplicity and ease make them available in a short time, at little expense, and not too remote from the practice of medicine.

Material for morbid anatomical investigation is obtained by *biopsy* when it is removed from the living body; although this term is usually applied to the removal of tissue for microscopical diagnosis it can be used to cover the study of tissues removed surgically for treatment. After death the whole body may be available for *necropsy* or post-mortem examination. The difficulties and advantages of these must now be considered.

1. BIOPSY. Submitting patients to surgical procedures is possible only on a limited number of occasions, and only a limited amount

of tissue is generally available; some tissue cannot be sampled at all. The time of the disease at which the sample is taken may, however, be early, and the tissue free from secondary changes; sometimes it is possible to repeat the examination. The tissue is fresh and can be handled as required; it can be fixed for microscopical study, but this should not be done until it is certain that chemical and bacteriological studies will not be wanted.

The most important disadvantage is the sampling error that may result from examining only a small piece of tissue. If the changes in the organ are diffuse and uniform throughout it may revolutionize our conception of a disease (see infective hepatitis, p. 184); it may assist our study of disease processes in which we never or rarely see cellular material; it should provide firm clinical diagnosis of the part sampled, if it is taken with experience and skill, but not necessarily diagnosis of the whole disease. It can never be relied on for the exclusion of a disease; a negative biopsy is only strong presumptive evidence of the absence of whatever is suspected, and that only if selection of the area submitted to microscopy by both surgeon and pathologist is skilful, the tissue is properly handled, and properly labelled—a point of such practical importance that it is justifiable to include it in a textbook on principles. Mistakes in pathological diagnosis are much more often due to bad choice of tissue to remove, inadequate fixation and careless labelling than to mistakes in microscopy.

2. NECROPSY. The study of the body after death has two purposes—

1. What may be called the medico-legal attitude: *the determination of the cause of death.* This may be extremely simple and only a brief glance at a few organs may give the answer. If the disease is one which causes chemical changes only, it may be quite impossible to find the cause, even with a good deal of clinical information.

It is usual to consider the cause of death under three divisions—

The *immediate* cause: why the patient died today and not tomorrow. This will often be an incidental complication of the main disease, e.g. broncho-pneumonia terminating a prolonged nervous disease.

The *principal* cause: why the patient died now and not in ten years. This is the most important part of the chain of causes to get right. Death certification in civilized communities and the international statistics of diseases are based on this, and it is most desirable that certification should be accurate, or the whole elaborate structure of epidemiology will be unsound.

The *contributory causes* should be looked for and recorded; they

will help to explain deaths in which the first two findings seem inadequate.

2. What may be termed the scientific attitude: *the collection of evidence on all disease processes* going on in the patient's body, not merely the fatal one, and certainly not merely those which are advanced. Some of the most interesting parts of a pathologist's work deal with the study of the earliest possible stages of disease, seen as trivial intercurrent findings in bodies dead from any cause, and perhaps most important in healthy people meeting accidental deaths. This is an inexhaustible and prolonged business.

There are a few disadvantages: permission may not be granted to make a complete examination, or even to make one at all, though limited incisions are rarely objected to. There is always a lag of at least an hour or two before the examination can be conducted, and often much more; during this time post-mortem changes will have begun, reducing the value of the technique progressively until only the grossest structural alterations can be made out; this deterioration is lessened in cities by refrigerated mortuary accommodation. The second defect is that only one examination of any stage of the disease is possible—not necessarily a terminal one, if the importance of intercurrent findings is not allowed to be blotted out by the search for the cause of death. On the other hand, the whole body can be examined more completely than at any other stage of the disease, and multiple samples can be taken for examination. Bacterial examination is rarely profitable, as many non-pathogenic saprophytic organisms swarm over the organs soon after death, but with precautions it may be successful and should never be forgotten.

The opportunity for chemical examination of post-mortem tissues is relatively rarely taken, and is not a routine part of the examination. It is a source of information as yet untapped.

4. Experimental Animal Pathology

It would be difficult to overrate the advantages that have been gained in the treatment of human disease by the study of the experimental animal. There are certain limitations; the most important relate to the differences between the human species and the common laboratory animals, and even between the animals themselves. Thus the nutritional requirements of rats and guinea-pigs differ; the latter can be rendered scorbutic by Vitamin C deficiency with ease, the former depend hardly at all on vitamin C in the diet. The pathogenicity of bacterial species varies greatly for different animals; if the wrong one is chosen, the results of the experiment may be quite misleading. The average age of the laboratory animal, and

the stresses in its life, are not comparable to the human; the reproductive habits are quite different; the limb muscles and joints have no weight problems worth mentioning. Difficulties of expense and size hinder the use of large animals and of monkeys, and difficulties of sentiment over the use of dogs, cats and horses have raised a barrier of legal provisions which must be satisfied before any animal work at all can be done. Few experiments have a time scale which bears any relation to the slow and gradual progress of most human disease.

Against most of this there are the great advantages that numbers of animals can be used to permit statistical analysis of the results and the animal can be killed as necessary at any stage of the disease which it is wished to observe. The methods of observation in general are those of the first three sections of this chapter, with the emphasis rather on morbid anatomy. Dangerous or lethal experiments can be carried out, for example with radioactive isotopes, which cannot be risked on human volunteers. The species difference, however, can only be finally overcome by the use of humans, when previous exhaustive experiments have shown animals to be unsuitable, as was recently done in the study of infective hepatitis.

It can be said in summary that animal experimental observations are always desirable, and often essential, but before their results can be transferred back to the human being they must be evaluated with caution and compared with the changes seen at all stages in the human case.

The Microscopical Study of Cellular Behaviour

Since the average size of the cells of which the body is composed is well below the power of naked-eye vision, the use of a microscope is inevitable, and with it the use of preparatory methods which greatly modify the cell studied. With special care and low-power objectives, studies can be made on living exposed cells in their natural environment; if cells are grown in tissue culture in thin films, quite high powers can be used and much detail seen in living cells by phase-contrast and interference microscopy. But in general, cell appearances are studied in the artefact form of thin stained sections of dead tissues, and the artificiality of this conventional description of cellular appearance must never be forgotten. The artefacts produced are on the whole consistent and not unrelated to what is seen by special methods in living cells, and they are far from useless, but they obscure the fact that the cell is a living and moving organism and not a thin flat red and blue plate.

Much higher magnification is obtainable by electron-microscopy,

again at the cost of some artificiality; the cells must be fixed, vacuum-dried, and cut into even thinner slices. The density of these sections is so low that it may have to be increased by depositing a coating of heavy metal over the section before it will show up. But much striking knowledge has already emerged from photographs so made, both on relatively permanent extra-cellular structures like flagellae, basement membranes and bone, and also on the internal features of the cell such as mitochondria and nuclear detail. It is still not easy to relate the structures so visualized with the chemical molecules of which they are made; indeed the functional studies made on whole or fragmented living cells have added more to our knowledge of the chemical processes by which these cells carry out their functions. The linking up of observations on structure and function at the near-molecular level is likely to bring even greater knowledge in the future.

Three other points are worth emphasizing if any real value is to be obtained from histological sections. First, the section represents a single frame from a continuous cinematograph picture, the state of affairs at one time in a continuous process. Each cell you see is doing something, has come from somewhere and is *en route* for somewhere else; the materials with which it is carrying out its functions are often visible round it or in its cytoplasm; the first steps in pathology come from recognizing these points chemically as far as possible. The mere identification of the cell is valueless unless there is further thought about why it is there, what it is trying to do, and what chemical tools are available for it to do it. Recognition of a cell as of a given described type is of some help in that the functions of some of these are known; it can be confidently assumed that the presence of polymorphonuclear leucocytes in numbers means an inflammatory response even if phagocytosis of bacteria cannot be seen. It is perhaps too easily assumed that cells which look alike must be alike—the histological patterns visible are limited in number and may be compared to looking at people at a distance. On the whole the appearance of cells is more dependent on what they have done than on what they are going to do, and there is no certainty that they must always retain their appearance in one form for identification purposes.

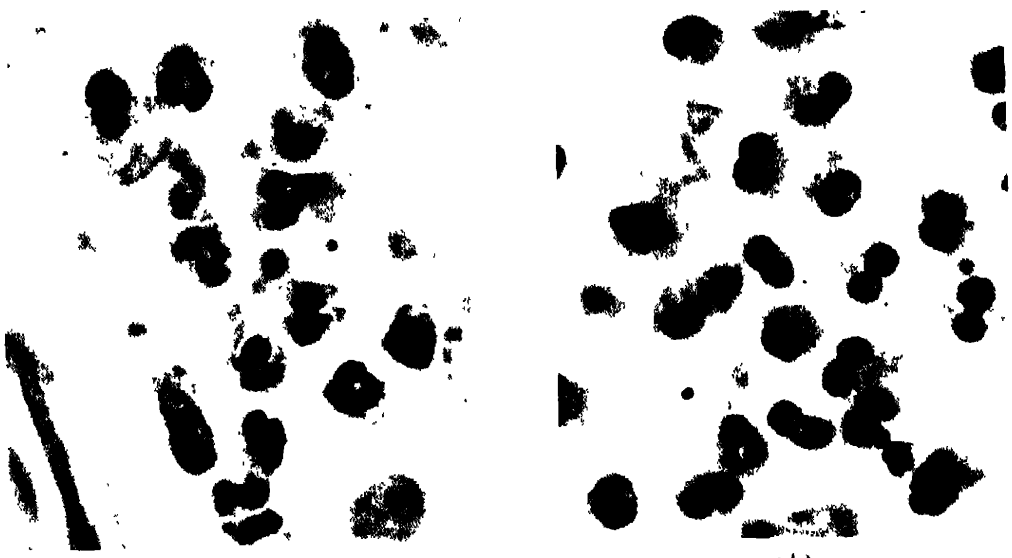
Secondly, the colours used in histological staining to make microscopical objects visible and identifiable have always a definite chemical basis, and the more definite this is the more valuable the section. The older techniques still in common use are the less specific, and the precise chemistry of many techniques is still not fully established; but if an exact chemical test is available in any

Plate 1. Inflammatory Cells

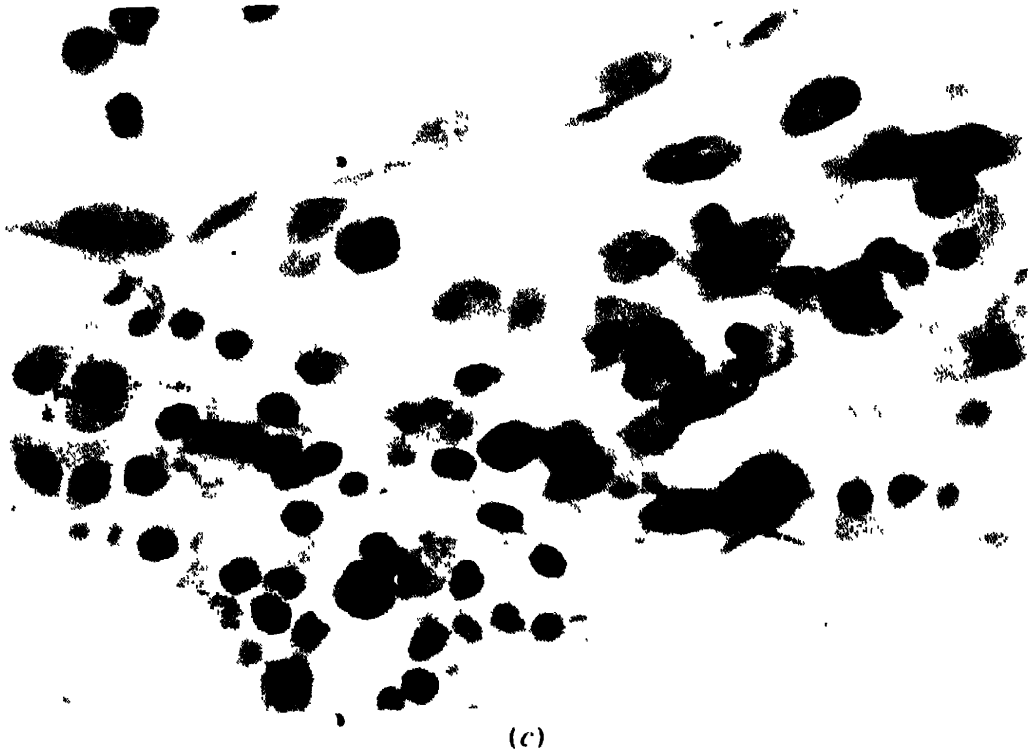
(*a*) (*b*) Polymorphonuclear and eosinophil leucocytes. × 960. The lobed nuclei of the polymorphs (*a*) contain three or more segments in the fully mature state; the cytoplasm is only very finely granular and very pale eosinophil. The eosinophil leucocytes (*b*) never have more than two-lobed nuclei; their granules are large, round, conspicuous and refractile, so that they are recognizable even in the absence of the eosinophil staining.

(*c*) Lymphocytes and plasma cells. × 850. The large cells in the upper right part of the field are typical plasma cells; oval, deeply basophil, apart from a zone of pallor near the nucleus at the position of the Golgi body; the chromatin is disposed in the nuclei in well-separated lumps (" clock-face " or " cart-wheel "); cytoplasm is abundant. The lymphocytes below and to the left are little more than a solid round nucleus. At the top, capillary endothelium lies across the field, with serum and polymorphs—one a little out of focus.

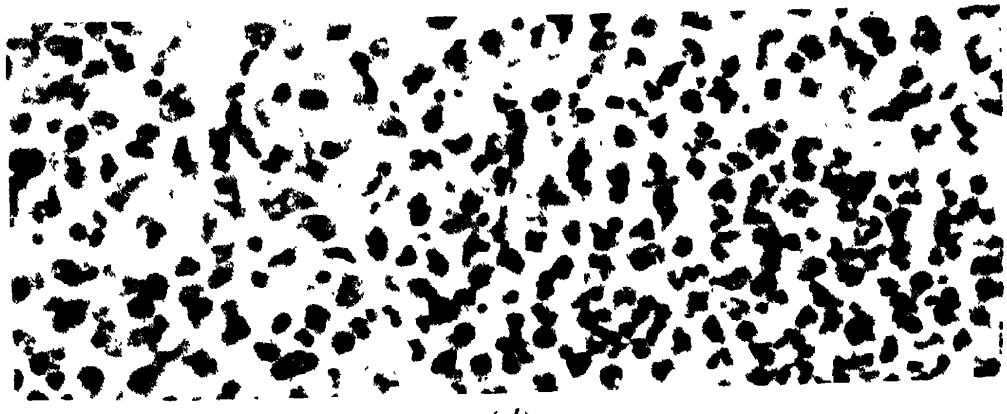
(*d*) The edge of an abscess. × 235. At this lower magnification the nuclear pattern of numbers of polymorphs (many dead and digested in the abscess) is clear, though the granules cannot be seen. The right half of the field is pus; on the left in the wall of the abscess there are about as many macrophages as polymorphs. Although recognition of pus is possible and should be practised at this magnification (which is low enough to allow search over a section) the higher power should be used to confirm the observation.



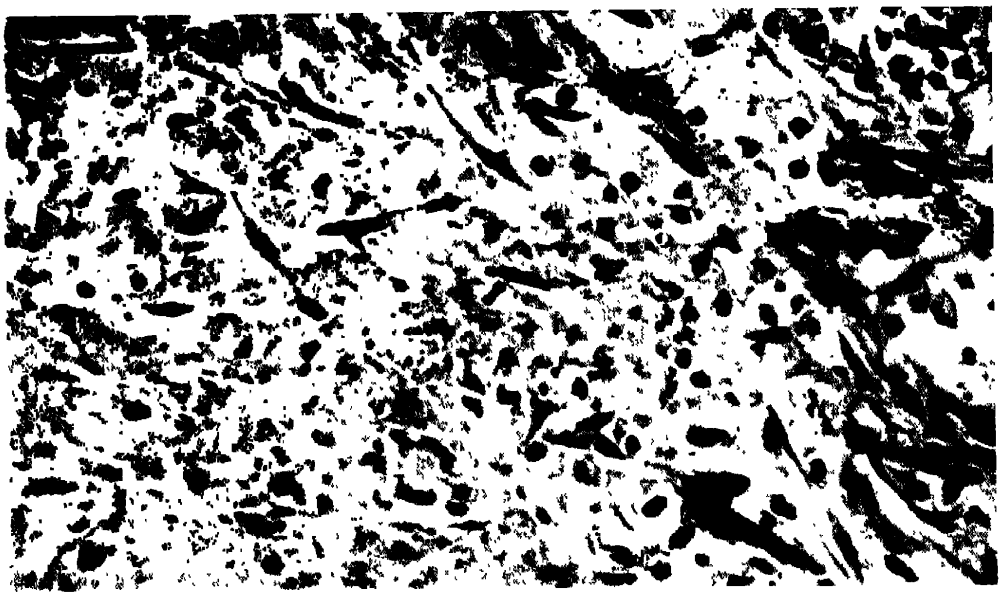
(*a*) (*b*)



(*c*)



(*d*)



(*a*)

(*b*)

PLATE 2. ASEPTIC GRANULATION TISSUE

(*a*) Early stage of invasion of fibrin (to the left) by fibroblasts and macrophages. Between the darkly stained capillary buds to the right can be seen macrophages, many with foamy cytoplasm, and the nuclei of fibrocytes and other cells. Further to the left elongated fibroblasts have migrated into the fibrin, which is partly digested and so stains less intensely than it does at the extreme left. Cell division in these migrant phagocytes is shown by the mitotic figure at the bottom left. Polymorphs are few, since there is no bacterial infection. The manufacture of fatty material from fibrin is of theoretical interest, as fibrin is a possible source of atheroma (p. 135). × 300.

(*b*) More mature young fibrous tissue. Elongated fibroblasts, with fine collagen fibrils associated with them, lie more or less aligned in the direction of strain. At this stage (the tenth day of a surgical incision) the macrophages and polymorphs are no longer in evidence in aseptic inflammation. × 300.

(*c*) Scar stage of a skin incision. × 110. The skin surface is just visible above to the right—a simple keratinized epithelial layer with no appendages. Dense rather acellular fibrous tissue lies below, with bundles of fine parallel fibres; this is contrasted with the coarse bundles of the original collagen to the left. Elastic fibres (black) are present here, but absent from the scar. Almost all the acute inflammatory cells are now gone (seven weeks after the incision) but some fibrous tissue nuclei are still visible.

section, use it, and as far as possible, think of alterations in appearance as having a chemical basis even if this basis is not yet capable of exact formulation.

The last of these essential preliminaries is to realize what a minute sample of the tissue lies in the field of your microscope. You may be attempting to elucidate the behaviour of a four-pound organ from a sample the size of a pin-hole and a few micra thick, if you do not make it a rule to use the naked-eye and low-power examination of your section first, and examine as large an area and as many sections as you have time for. The worst way to practise pathology and the surest route to error is to regard the " pathology " of a given condition as dark-blue dots seen in a glance down a high-power objective. With these warnings the study of stained sections, which is really the only practicable method for medical students with limited time and limited cost of training, is a valuable and safe guide to cellular processes.

It is probably wise to add the warning that until considerable experience is gained intra-cellular detail is better ignored. The range of artificial variation is great, and minute changes are as yet not clearly related to physiological abnormalities. Minute spots that can only be seen with the high power are more likely to be dirt or precipitates than pathogenic bacteria. Use the high power for the precise confirmation of the identity of cell types whose distribution you have mapped out with the lower power, and for the presence of properly stained nuclei; many other instances of cytological details which can be reliably noted will occur in these pages, but in most cases the detail is large, or conspicuously stained, or appears in a large number of cells so that it cannot be missed. If the appearances in one cell puzzle you, look at another one; only if it is widespread is minute detail likely to be significant.

The Internal Detail of the Cell

Although the advice in the preceding paragraph is applicable to medical students starting the subject, this is only because of the difficulty of distinguishing between artefact and reality in minute intracellular detail. From the research point of view, the frontier of knowledge is now the internal structure of the cell, the morphological description of it as a unit being now pretty well worked out. Much intracellular detail is known and described; the accurate maintenance, in the face of changing external environment, of a standard appearance and complex metabolic changes presupposes that inside the cell each molecule and enzyme has its appropriate position; the internal anatomy of the cell is probably at least as

complex as the gross anatomy of the entire body. Some of the structural evidence for this is found in the description of mitochondria, Golgi apparatus, microsomes and the like; the association of these bodies with enzymes is often proved, as for example the mitochondria and phosphatases, by differential centrifugation experiments. The cytoplasm must not be regarded as a single-phase material or a haphazard jumble. The metabolic disturbances in the deranged cell—which lead in the end to the visible changes of descriptive pathology—must take origin in these enzymes and the structures containing them. The future of handling these damaged cells will turn on knowledge of these details, at present too involved and difficult to deal with in the space available in this book for elementary students; but we must end this section with the saying of W. B. Hardy: " the outward and visible changes in cells are the expression of changes taking place in internal and invisible chemical places."

REFERENCES

Technical details are best learnt practically; there is no point in committing them to memory until the technique is actually required. Since in general a good deal of experience is necessary before accurate results will be obtained, most pathological work is now studied as a post-graduate specialist training. But the student should have the necessary knowledge to interpret the reports, and should know the outlines of the methods and what they are attempting to show, and how to obtain the necessary specimens and preserve them if required.

The principal normal values of most substances estimated in blood and other fluids will be found as an end-paper.

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This book gives a discussion of the values of the tests and the indications for them as well as the normal ranges.

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CHAPTER 3

INFLAMMATORY RESPONSES

THE definition of inflammation is " the local reaction of the tissues to injury." The causes may be divided immediately into—

1. Non-living agents: mechanical injury; heat and cold in excess, and other radiations; chemical substances acting directly on exposed cells.

In this group, the damaging agent is confined to the site affected; its effects are at their worst at the start. Repair stages can begin at once from healthy surviving adjacent tissue.

2. Living agents: the size of these varies from metazoa such as the larger parasitic worms which are easily seen with the naked eye, through protozoa and bacteria which can be seen with instrumental aids, to the smallest living organisms—the filter-passing ultra-microscopic viruses.

The term *bacterial* is used somewhat loosely to cover this group; *micro-organismal* would be more correct but is cumbersome.

The important differences in this group are that the damaging agent can grow, multiply, move or be moved to adjacent or remote parts of the body; it may excrete powerful poisons which will be absorbed into the blood-stream and may cause effects in distant organs; the primary attack may be by an insignificant number of bacteria, and the disease may occur only after a period of incubation during which the population of invaders is increasing to numbers which can overcome the defences of the body; this time may vary from hours, in meningococcal meningitis or plague, to years in leprosy or tuberculosis. The damage is not at its worst at the start, and the agent can spread into the tissue that is attempting repair and render this ineffective.

As always in pathology, these two groups may be combined. The commoner event is for the burn or cut of the first group to acquire secondary infection with micro-organisms; but from time to time you will see bacterial infections of the skin or urinary tract treated (usually by laymen) with such enthusiastic chemical antisepsis that a secondary chemical burn results. The point then arises that the

layman is apt to think that the treatment is too weak to be successful and make matters worse by increasing the dose.

To these events the answer of the body is an active process which normally has the result of stopping the invaders and repairing the damage done; to this active process the name *inflammation* was given long ago because in its most obvious forms the part affected is red and hot. But many of the most successful inflammatory responses are those in which the invaders are suppressed at the start with little or no heat; there is every possible gradation of response, and it is usually proportional to tissue death. It is at its least in the healing of an aseptic surgical incision, and this is the simplest case to describe. When there is bacterial infection the reaction becomes so much more severe that it is convenient to treat it separately.

We have, therefore, to consider three main heads—

1. Acute aseptic inflammation, due to non-living agents.
2. Acute infective inflammation, due to living agents. Of this group there are many varieties, depending on: (*a*) the part of the body involved and (*b*) the type of micro-organism involved.

These are active responses, much more often than not successful in repelling the invading organisms and repairing the damage done. In a minority of cases, the response is not rapidly successful, the inflammation prolonged and the result uncertain. This makes the third group.

3. Abnormal inflammation. Here there are sub-divisions again: (*a*) chronic inflammation due to (i) anatomical causes and (ii) bacterial causes; (*b*) allergic inflammation, where the abnormality lies in the individual; (*c*) special cases—inflammation in bones and joints, in the central nervous system (C.N.S.); the reactions to radiations; and the changes in the inflammatory reaction brought about by modern drugs. Abnormal inflammation is considered in Chapter 4. The details of the first two types must now be filled in.

Acute Aseptic Inflammation

This simple, important and fundamental process has been very thoroughly investigated since the days of Lister and Metchnikoff, but there are still many details incompletely explained. The process is an extremely common one; no one passes a month without healing some slight cut or graze; it is as physiological and essential a process as digestion, and the first main point is that it is as reliable and successful. If it were not so, there would be no surgery; but we can recommend surgical treatment to our patients in certain

confidence that acute aseptic inflammation will heal incisions. There are a few cases where the process is unsuccessful; a small number of people heal badly, for reasons which we can often foresee and will discuss later; but it is important to realize that they are exceptions.

Investigation of this process in detail is usually carried out in animal experiment, for the process appears very similar in all mammals and some lower creatures; the mesentery of the frog is transparent and both this and the web of the foot were used by the pioneer studies of Lister and Metchnikoff. More recently transparent chambers (Clark–Sandison chambers) have been inserted in the ear of the rabbit and the detail observed in the living mammal. Parallel studies using human tissues excised from a series of patients at varying times after injury and examined histologically have shown that the animal observations are closely related to those in man (Plates 1-5). The sub-divisions of the process are (*a*) the *exudative phase* followed by (*b*) the granulating or *repair phase*.

(a) Exudative Phase

The events observed are—

BLOOD-VESSELS. After a momentary stoppage with contraction of the capillary wall, there is a dilatation with consequent stagnation of the flow in the vessel. The streamlined flow of the cells changes to an irregular drift in which the cells adhere to the wall; gaps occur in the wall through which red corpuscles can be seen to be carried, and the polymorphonuclear leucocytes migrate actively. There is an escape of protein-rich serum into the tissue spaces. The effect of spasm and contraction is the more important if an artery is involved in or near the injury; while this may obviate loss of blood, it may starve parts supplied further on the vessel's course, and hinder healing at the site of injury.

If there is a break in the vessel wall, there is an escape of blood which clots and so seals the breach. The fibrin has a further important function that it forms a scaffolding on which cells carry out the two functions of *phagocytosis*, i.e. the ingestion and disposal of dead tissue and other materials, and *movement*—cells creep over a surface better than they swim in a fluid.

There is an emigration of two important phagocytic cells—the *polymorphonuclear leucocyte* and the *macrophage*, the numbers of which are related to the amount of dead tissue requiring removal, and therefore are few in a simple incised wound, where tissue damage is minimal.

(b) Repair Phase

This is a proliferation of cells, rather than an accumulation of material and pre-formed cells, and therefore takes time. It follows about twenty-four to forty-eight hours after the exudation, with which it is for a time mingled until all dead tissue is removed and then is seen alone. The proliferating cells are collectively called *granulation tissue*, from the pink granular appearance seen in a clean wound where an area of skin is lost; cells from the previous stage are present at first, but the important components are—

FIBROCYTES: these migrate along the fibrin strands and so follow the alignment of the fibrin along the strains in the wound (well seen in the healing of tendons) and give the fibrous tissue the orientation necessary to hold the edges of the wound together. They are at first large cells, histologically much like macrophages, but declare their identity by formation of collagen fibres; they are dependent on adequate amounts of vitamin C.

CAPILLARY BUDS grow out from the neighbouring blood-vessels and support these fibrous cells and ultimately the surface cells.

SURFACE CELLS finally heal the breach, growing from the edge of the wound into and under the clot, first as a single layer gradually differentiating to form the epithelium proper to the part, but often somewhat imperfect; skin for example forms a strong keratinized epithelium, but does not re-form hairs, sweat or sebaceous glands.

When a simple incised wound heals in a straightforward manner according to the above description, without the edges becoming separated once they have been brought into apposition, it is referred to as healing by first intention; the time taken varies from about four days in a wound of the face in a young person to as many weeks in the leg of an old one; it is dependent on the blood supply; nothing is known which will hurry the process on.

Since this inflammatory response is dependent on blood supply, it cannot occur at all in an avascular tissue, such as cartilage—the torn meniscus of the knee that is a common football injury is a good example. Fibrous tissue is formed readily in any part of the body in the later stages of inflammation; all epithelia can be relied on to regenerate and cover breaches; internal organs vary in their repair; thus adipose tissue is not regenerated; liver cells and renal tubular cells regenerate readily; observations on the regeneration of other solid organs are rarely made. Muscle regenerates, but usually inefficiently since there are no properly adjusted sarcolemmal tubes for the downgrowth of the new fibres; the same holds for the axon growing out from the cut end of a severed nerve—if the neurilemmal

tubes of the distal end (which do not degenerate) are correctly aligned and closely co-apted to the trunk, or if the injury does not interrupt them at all, recovery though slow (1 mm/day) will be complete; if there is disorganization at the cut, a useless mass of tangled axons will form in the fibrous tissue (amputation neuroma) but there will be no recovery.

BURNS are a special case of acute inflammation of great importance because of the extent of tissue damaged, in surface area and in depth. From the burnt area a copious inflammatory exudate acts both as a favourable culture medium for incident bacteria and a cause of extremely significant fluid loss, of plasma and water; toxic absorption is likely to be serious. For these reasons extensive burns are commonly fatal; and the damage to the deeper layers under the skin interrupts the process of healing. Epithelial spread from the uninjured margin is therefore slow, and grafting methods may be required to get speedy coverage.

Acute Purulent Inflammation

This is exemplified by the common boil, due to infection with a staphylococcus; many other micro-organisms set up similar events. The main differences here stem from (*a*) the much greater tissue damage, which leads to the formation of much more exudate, rich in polymorphonuclear leucocytes and known as *pus*; (*b*) the bacteria present are capable of growth and possibly of movement, and so can increase and spread the damage; (*c*) a chemical defence mechanism is brought into play in addition to the cellular one.

Factors Tending to Limit the Inflammation

The exudate in the first place is a vehicle for carrying about the bacteria, but if it is fibrinous and rapidly clots, mechanical transport is hampered. The exudate then acts against the bacteria in two ways—

1. FIBRIN BARRIER. This is not only a mechanical obstruction to bacterial movement but a chemical barrier with selective permeability which stops the diffusion of products of bacterial metabolism and destruction—toxins—into the rest of the body. This can be shown by watching the diffusion of coloured dyes, of molecular weight and charge comparable to the toxins, out of an inflamed area, and comparing the rate with that from a less fibrinous inflammation.

2. ANTIBODIES. The body has the capacity to reply to the invasion of the tissues by any protein, the reply consisting of the formation of another protein, with the characteristics of a globulin, which with

extreme specificity combines with the first protein to form a larger molecule, often a visible precipitate. These principles apply whether the original protein, to which the name *antigen* is given, is a chemical substance, a bacterial toxin, a bacterial or virus body, or other invader. The protein formed in reply, known as the *antibody*, is formed in macrophages and lymph nodes draining the inflamed area; it is quite extraordinarily specific, so that it will sometimes react only with an individual strain of bacteria or with a protein molecule which cannot be distinguished chemically from others with which the antibody does not react at all; and it takes some time, about ten days, to appear from the first contact with the antigen. Once present in the body, the antibody persists for some months, and the capacity to make it rapidly when the body is again challenged with the original antigen persists almost indefinitely. When, therefore, the body meets an invading organism with which it has previous acquaintance, antibodies in the serum will be quickly available; even with new organisms they are fairly quickly made. The details and complexities of the subject are dealt with in the companion volume on Bacteriology.

When antigen and antibody react, the proteins are clumped and the bacteria agglutinated into masses. This not only stops their movement, but renders them more easily destroyed by phagocytosis (opsonic effect) and in normal serum by spontaneous solution or lysis; toxic protein products are similarly rendered inert.

3. ANTI-BACTERIAL SUBSTANCES from living or dead cells. These include haem, lysozyme, and possibly lactic acid.

4. PHAGOCYTOSIS. The ingestion of bacteria by the two phagocytic cells is the most important method of destruction; aided greatly by antibodies, it is an essential step in finishing off the invasion without which antibodies are not completely successful. The ingested bacilli are sometimes killed, sometimes not—the gonococcus for example divides several times inside the polymorphonuclear cell, though it is a delicate organism culturally. If the leucocyte lives, it can move away with the bacteria, but many of the most common organisms, e.g. the pyogenic staphylococci, contain *leucocidins* and kill the leucocyte.

Factors Favouring Bacteria

1. Their capacity for *growth* and often also for *movement* has been alluded to. In addition, there are the *movements of the living patient* (both those of voluntary muscles and those dependent on the cardiac pulsation in the tissues, respiratory and peristaltic movements) which are responsible for distributing bacteria locally, particularly

in inflammations in which there is a large effusion of fluid, up to the time the fluid clots. An additional power of traversing the tissues is given to bacteria by unsuccessful phagocytes, which can move some distance before dying.

The capacity of living inside a cell is shown by many organisms; protected by the phagocyte from antibodies and drugs in the tissue fluids and yet not destroyed by it, the organisms often cause chronic or recurrent infections. They gain this capacity at the expense of the ability to live out of the cell, and culture of these organisms is often difficult (or even impossible). Examples are the organisms of brucellosis, leprosy and tuberculosis.

2. TOXIN PRODUCTION. The poisonous substances produced by bacteria are undergoing exhaustive analysis at present; this has resulted in great clarification, for the action of many of these toxins can now be expressed in the terms of enzymes and not of vague complex substances with a number of unexplained actions on the body. The list of enzymes making up the toxin of individual bacteria is, however, often a long one; thus at least eight enzymes have been extracted from the organism which causes gas gangrene (*Clostridium Welchii* and other species), including a collagenase, a hyaluronidase, and a lecithinase, each breaking up part of the tissues and combining to make the organism a most dangerous invader. There are still many other toxic products extractable from bacteria the part played by which in the ordinary processes of inflammation is uncertain, and the chemical description of the toxic actions of bacteria on the tissues is far from complete.

Between these two groups of factors a balance is struck and on the result of this will depend the outcome—the destruction of the organisms, the formation of pus, or indefinite spread and generalization of the infection until the patient dies. As before, by far the commonest result is healing, with or without suppuration; the restitution of normal is known as *resolution*. This occurs in the common trivial skin infection known as a "blind boil"; a more important example is the recovered case of lobar pneumonia (see p. 44).

SUPPURATION or the formation of pus is common enough; when the pus is contained in a cavity it is known as an *abscess*. This results from the accumulation of the fluid exudate and the phagocytic cells with their contained living or dead bacteria. Proteolytic enzymes are liberated by the phagocytes which digest the fibrin, dead tissue and dead leucocytes into a thick yellowish or greenish material, the colour being provided partly by pigments derived from the bacteria,

e.g. the greenish-blue pus containing *Pseudomonas pyocyanea*, and partly by products of haemolysis from traces of blood in the cavity. Films made from pus will always show the characteristic lobed nuclei of polymorphs, though often they are very badly preserved (Plate 1); pus-like material which does not contain polymorphs is found in tuberculosis and breaking-down growths. The bacteria may be seen and cultured from the pus, but they may die out or be few. Around the purulent cavity is found a zone of granulation tissue much like that in a healing incision except for the persistence of large numbers of inflammatory cells. The accumulation of pus in the tissue spaces under tension causes pain, and the pus is usually evacuated by incision as soon as the enzymes have had time to digest it to a fluid consistency; it may alternatively make its own exit through a skin or mucosal surface; or it may become encapsulated. If liberation is inadequate, the consequence is usually chronicity, discussed in the next chapter

After the evacuation of pus the walls come together, and the cavity fills up rapidly with serum and granulation tissue, which tends much more to that seen in aseptic conditions, though a few inflammatory cells usually persist. This in turn is replaced by scar tissue.

Spread

1. LYMPHATIC SPREAD. This is a very common event even in controlled inflammations; most people have had tender glands with streaks of red in the subcutaneous lymphatics leading to them from some septic scratch or other injury. The tissue spaces drained in the ordinary way by the lymphatics are similarly drained when they are distended with inflammatory products (all protein in tissue spaces appears to return to the blood by the lymphatic system); and along with these are carried numbers of bacteria. In the gland the same processes of inflammation take place; there is a large number of phagocytic macrophages in the walls of the sinuses of the gland and these multiply and become conspicuous (Plates 4, 16); this in mild infections is referred to by histologists as " sinus catarrh " but goes on in the worse examples to frank purulent inflammation and abscess formation. The process may spread from one gland to the next in series or it may go from gland to the blood-stream.

2. UNOPPOSED GENERALIZATION. A small number of pathogenic organisms are held very poorly by the body; examples being those of anthrax and plague. In debilitated people commoner organisms may similarly run wild, producing a *bacteriaemia*, i.e. colonization of the blood-stream by the organisms. In general this is a transient

affair, the organisms being swept out of the blood by the macrophages in the spleen, bone marrow, lymphoid tissue, liver and elsewhere. Persistent bacteriaemia implies either the inefficiency of these, so that the blood is recolonized—a fatal condition; or else a *pyaemia* in which the bacteria have a foothold in blood-clot, usually a vein in the inflamed area, sometimes a clot adherent to the heart-valves; this forms a focus in which the organisms can multiply untroubled by either the cellular or humoral defence mechanisms of the body. The clinical term *septicaemia* and the laymen's *blood poisoning* are inclusive terms covering both of these possibilities without particularizing; *toxaemia* signifies the presence in the blood-stream of bacterial toxins only.

3. TOXAEMIA. Under this regrettably vague heading come chemical disturbances due to the absorption of products of bacterial metabolism or the inflammatory exudates which lead to *fever or pyrexia* in the patient, and to loss of appetite and a feeling of illness, to which pain from the abscess contributes its quota. Although the mode of action and chemical nature of these substances are not known, there is no doubt of their reality if a patient is under observation before and after the evacuation of a considerable amount of pus from, say, a pleural cavity (see also Chapter 6, p. 179).

4. SPLENOMEGALY. In all bacterial infections of the blood-stream, and in some inflammations where the bacteria are not actually demonstrated in the blood-stream, splenic enlargement to about twice or three times the normal size is observed. This is due to the proliferation of phagocytes in the walls of the splenic sinuses and accumulation of phagocytes there from elsewhere; the bacteria may be cultured from the spleens at autopsy. In the most acute infections the enlargement is slight and the soft inflamed spleen is not easy to feel; it is so vascular that it is red when cut across at autopsy, i.e. the acute or red septic spleen. If the patient lives longer and the infection is chronic, there is less blood and more cellular infiltration in the organ; it is larger, harder and more easily palpable, and grey at necropsy, i.e. the chronic septic spleen. Antibody production goes on in the spleen when antigenic material is in the blood-stream.

The General State of the Patient; Resistance

This plays a part in determining the reaction of the patient to any infection; even the most overwhelming, like plague in England in 1665, spared some of those infected. This resistance is not wholly tied up with fitness in the ordinary bodily or athletic sense, but the factors determining it are not all clear. Most important is the presence of pre-formed antibodies. The typhoid bacillus can be

injected dead and still act as an antigen; the antibodies formed as a result of this prophylactic inoculation cut to a hundredth the risk of contracting the fever or dying from it if contracted, as was shown in the troops in World Wars I and II.

The metabolic background includes such things as diabetes, fasting or starvation, exposure to cold, oligaemic shock, all of which can be shown experimentally to lower resistance. The biochemical mechanisms at the back of the inflammatory responses are sensitive to abnormal metabolites like the keto-acids found in diabetic coma, which by upsetting reversible mechanisms may release an infection apparently dormant. Even psychical states, acting by way of the general metabolic background of the body may play a part in permitting infection. The dramatic local events in an inflamed area must never divert your attention completely from the rest of the patient.

Sources and Reservoirs of Pathogenic Bacteria

The relevant pages of the volume on Bacteriology should be consulted here.

The Cytology of Inflammation (see Plates 1-4)

In the exudative phases two very important cells are dominant, the polymorphonuclear leucocyte and the macrophage (histiocyte).

THE POLYMORPHONUCLEAR LEUCOCYTE. Formed in the bone marrow, these cells are normal inhabitants of the blood-stream (about 5,000/mm^3) but they are not normally present in the interstices of the tissues. This number is increased (leucocytosis) to 40,000 or more in response to globulins (as yet ill-defined) formed in inflammatory exudates. When they are present in the tissues in sections, they are a certain indication of acute inflammation, becoming more and more prominent the more tissue destruction there is. Their functions include *phagocytosis*, i.e. the ability to ingest micro-organisms of most kinds, though they do not necessarily kill those they ingest; *the liberation of proteolytic enzymes* which result in the liquefaction of fibrin and the dissolution of dead tissue; other chemical functions are suggested by the enzymes and substances detectable in the cells. The function of phagocytosis is in these cells confined to very small particles, notably bacteria.

THE MACROPHAGE OR HISTIOCYTE. This cell though perhaps less conspicuous is even more important. It is found in the blood-stream as the monocyte or large mononuclear cell (about 400/mm^3) and in an inconspicuous inactive form is widely distributed throughout the tissues of the body, normally in small numbers. In inflammatory

responses these cells are caused to appear and to multiply by stimuli which are as yet unstudied. Though in general there are similarities in function with the polymorph, there are important differences. It will be seen that there are fewer of these cells immediately available, and therefore the first emergency work will fall to the polymorph. The macrophage on the other hand is a much more effective phagocyte, ingesting not only bacteria but debris of all sorts and sizes, including red blood corpuscles, the nuclei of dead cells, and particulate matter; if this is too big for one cell to engulf, a group will surround it, often fusing in their action and forming a foreign-body giant-cell. The enzyme digestion of the macrophage is also more powerful, taking place both extra-cellularly, and intra-cellularly, the macrophage becoming distended with its meal and often forming a rounded cell with cytoplasm loaded with fatty material (*foam cell*); the fat may come from fibrin, pus, keratin or other less likely sources as well as from the fat tissue of the body or the lipids of the C.N.S.

Both these cells are highly motile, attracted by certain chemicals, and their phagocytic capacity is easily demonstrated *in vivo* and *in vitro*. As with the polymorph, ingested bacteria are not necessarily killed, and the power to live inside the cell is not related to the capacity to grow in the culture-tube of the bacteriologist, often the reverse; the easily grown staphylococci are killed, the delicate brucella survives.

THE LYMPHOCYTE. The part played by this cell has been difficult to elucidate. As seen in sections and in blood-films, it consists of a nucleus, densely packed with chromatin, surrounded with the merest trace of cytoplasm, in which no special structures are visible.

From the mass of nuclear material we can deduce that like the spermatozoon it carries the chromatin potential for very wide development of function; but there is no cytoplasm to show what that function is. We rely largely on cytoplasmic events and pericellular substances to judge what a particular cell is engaged on, and there are none of these to help with the lymphocyte. Moreover its wide distribution in the normal body and in an apparently haphazard collection of pathological events—principally loosely classed as quiet chronic inflammations—provides no pointers. They are motile, but slow starters; they are not phagocytic.

In the normal body they are found in the blood, in the lymph, in lymph-nodes, in the submucosa of the alimentary tract both in nodes and diffusely, and in the bone marrow. It can be shown that the amount poured into the blood-stream by the thoracic duct alone (which is certainly not the only source of the blood lymphocytes) is

sufficient to replace those in the blood five times daily. Tracer technique has shown that labelled lymphocytes leave the blood in a few hours; their total life, however, in Clark–Sandison chambers is of the order of twenty-six days, during which time they remain unchanged. There is no evidence that they die in the blood-stream or are excreted; the disappearance of these immense numbers can only be explained by their metamorphosis into other forms of cell in various parts of the body, perhaps most conspicuously in the marrow, where they are mainly to be found; or by their return to the lymph nodes where most of the remainder of the labelled lymphocytes appear. If one assumes that their inconspicuous appearance is only the travelling cloak of a polyvalent reticulum cell, it fits in with what is known about them both in normal and pathological conditions; they have been seen to develop into macrophages in tissue culture. It is probable that they make their changes slowly, and may enter and leave the blood more than once. They are undoubtedly formed in the lymphoid tissues, though not only in the Flemming germinal centres, but this is not the only site of formation.

Their pathological importance is great. They are conspicuously concerned with virus infections; the giant-cell of measles (Plate 5) and the lymphocytosis in virus infections, including the unconfirmed virus disease glandular fever, rubella, and mumps; the virus of vaccinia can be carried by them, that of poliomyelitis possibly, and non-pathogenic viruses have been found in the lymphoid tissue of the naso-pharynx. The stimuli of their normal control are not known, but both clinically and experimentally the organism of whooping-cough alive or dead, *Haemophilus pertussis*, causes a most striking output of lymphocytes; and conversely, the adrenal cortical steroids depress them; these actions are on their formation, as shown by animal experiment, and not on prolonging their life or hastening their destruction. The possibility that the marrow lymphocytes are indeterminate stages of blood-cell precursors is unproved but not unlikely.

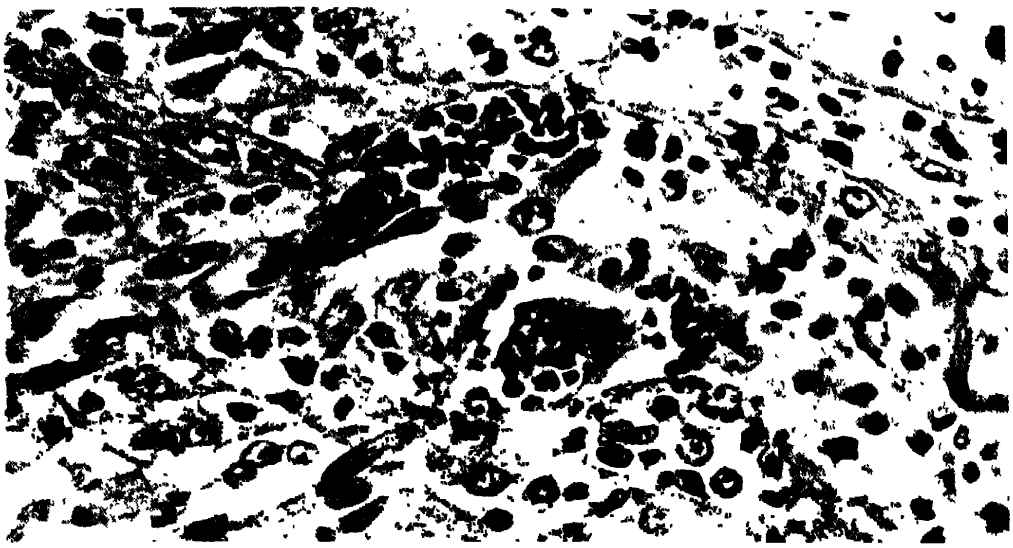
Because of their unassuming appearance, their frequent normal distribution, and the wide possibilities of their future intentions based on the concentrated nucleoprotein of which they are largely made, the recognition of the lymphocyte in tissue sections is not of the value that attends the recognition of the polymorph. When they are in company with plasma cells, macrophages, fibrous tissue, they add little to what is known from the presence of these cells; when they are present alone, it is conventional to speak of " chronic non-specific non-antigenic inflammation " and they are indeed often found when such inflammation is present. In other situations they

PLATE 3. PURULENT INFLAMMATION

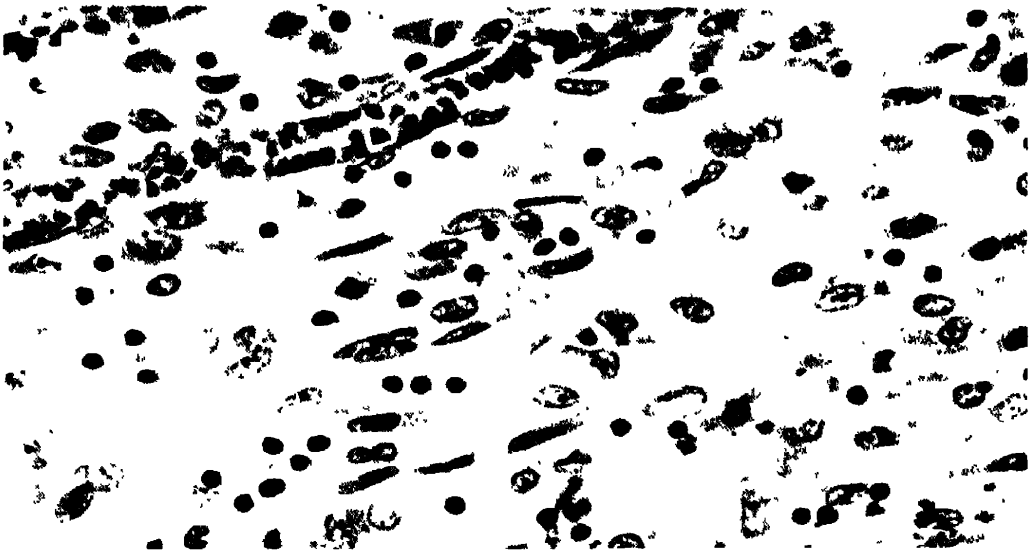
(*a*) Edge of a fibrino-purulent peritonitis. Coarse grey wavy strands of fibrin to the right, with polymorphs and some large mononuclear cells (probably macrophages) between them. This exudate is being organized from the left by granulation tissue made up of capillary buds (the red cells are nearly black in the photograph) and a varied population of macrophages, polymorphs and others; serosal cells are not now recognizable. × 350.

(*b*) Deeper (older) granulation tissue from a similar area. The fibrin has been replaced by granulation tissue in which two capillaries are conspicuous and many large ill-defined grey cells, whose big nuclei have a ring of chromatin and a well-stained nucleolus. These are mainly macrophages, but some of the flatter and more elongated cells are probably fibroblasts, and some may be capillary endothelial cells; they cannot be definitely identified with this stain alone. Also visible are many round black nuclei, most of them lymphocytes, but some plasma cells (e.g. near top right of the photograph). × 350.

(*c*) Chronic purulent inflammation (osteomyelitis). The paler part of the mass in the bottom right corner is a piece of dead bone (cell spaces empty), the infected foreign body that is responsible for the chronicity. On its upper border are osteoclasts removing it, lying in the characteristic erosion pits (Howship's lacunae); the upper right corner is occupied by granulation tissue—capillary buds, lymphocytes, polymorphs in the upper corner, and fibrous and other cells; this association is common, osteoclasts and granulation tissue. The fibrous zone of the reaction to the left contains a big group of dark-stained plasma cells, and bone formation is walling in a small pale fragment of dead original lamellar bone. The darker bone with conspicuous living cells in the bottom right is a similar attempt to wall off the big dead fragment; this has been involved in the granulation tissue (either by extension of the inflammation or movement of the fragment) and it is now being included in the erosion area by the osteoclasts above it. × 155.



(*a*)



(*b*)

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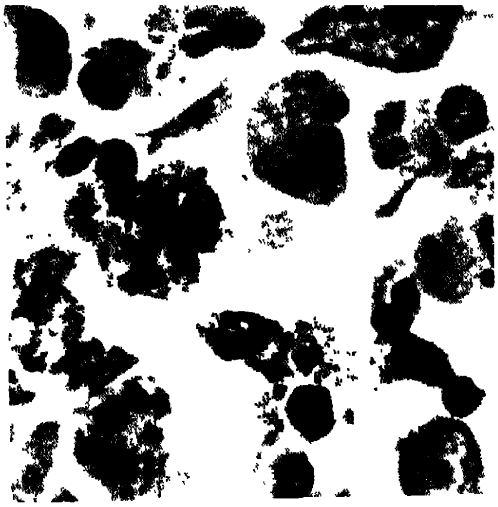

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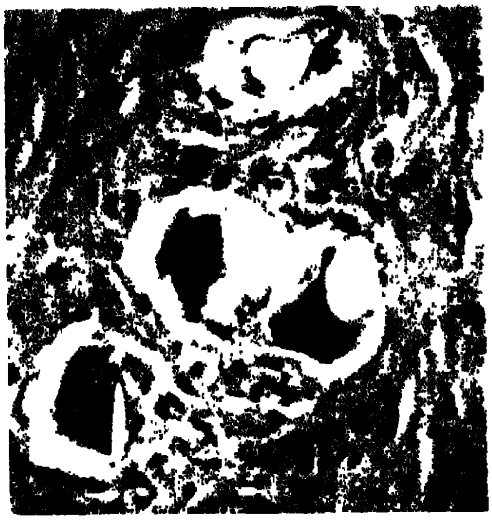

(*d*)

(*e*)

(*f*)

PLATE 4. MACROPHAGES

(*a*) Resting, in the peripheral sinus of a lymph-node. Stellate cells, with ill-defined pale cytoplasm and large nuclei, in which a good deal of detail can be seen. A lymphocyte present also, near the foot. × 1000.

(*b*) Phagocytosis. Dark ingested fragments of pyknotic nuclei of dead cells can be made out in these macrophages from an area of inflammation due to typhoid organisms in a lymph-node. × 1000.

(*c*) Phagocytosis. Large round macrophages with foamy cytoplasm in an abscess cavity, much lipid in the cytoplasm, formed by the cells from the break-down of pus (" foam cells "), and one has also ingested two polymorphonuclear leucocytes. × 400.

(*d*) Foreign-body giant-cells, around suture material (brightly refractile) in the scar of a surgical incision. Formed by fusion of macrophages or nuclear multiplication without cellular division, they are very common and conspicuous objects in inflammatory reactions to large particulate material. × 280. (See also Plate 5.)

(*e*) (*f*) Phagocytosis. Leprosy; lymph-node. × 1420. On the left, seen in a routine stain (haematoxylin and eosin); on the right, acid-fast stain. The enormous number of bacilli seen in (*f*) is completely invisible in (*e*); not only may the diagnosis of leprosy be missed if one relies on H and E sections alone, but this points out that it is quite likely that innumerable things are present unrecognized, because we do not know the particular technique which will show them. Note also that phagocytosis is not fatal to the organisms, which can multiply inside the macrophages.

can only be observed, and opinion on their actions reserved, with due respect to a powerful individual travelling incognito.

THE PLASMA CELL. Although often bracketed with the lymphocyte in pathological descriptions, this is a much more rewarding cell to recognize. It is invariably associated with the production of globulins, and more especially with the production of antibodies. Whenever it is present in sections, it is therefore evidence of the presence of an infection which has reached the duration of antibody formation, that is about one week or two, and so on the borders of a chronic infection; it persists while this infection is active; and this infection is antigenic. It is well seen in almost any chronic purulent inflammation, and in syphilis; it is much less conspicuous in tuberculosis, and it is not found in the vague quiet chronic inflammations where lymphocytes are common.

The morphological differences between plasma cell and lymphocyte are conspicuous (Plate 1c).* The origin is not quite settled. It can certainly be derived from macrophage-like cells found in the perivascular tissues; it can be formed in the marrow; it may well be formed from lymphocytes and in view of what has been said above this is probably true of an indirect formation.

THE EOSINOPHIL LEUCOCYTE. Conspicuous because of the intense staining of its large refractile cytoplasmic granules with eosin, this normal constituent of the white cells in the blood (at 400/mm^3) is easily seen in sections but much less easily interpreted. In three groups of conditions the number of circulating eosinophils rises to levels in the blood that are of diagnostic value: allergic conditions in general, including asthma and allergic angiitis (p. 89); infestation with parasitic worms; and certain skin diseases. In tissue sections, though their relation to these can still be seen, they are present in small or moderate numbers in many unrelated conditions.

CAPILLARY AND SEROUS ENDOTHELIA may proliferate but do not change their lining function

FIBROBLASTS are responsible for the formation of collagen in the repair stages. This begins early with very delicate strands of material which may take certain stains—notably ammoniacal silver—as basement membranes and the supporting fibres of the sinuses of lymph-nodes do, and is called reticulin. As the tissue becomes older, the cell nuclei become less prominent and the fibres thicken up till they form dense bundles and lose their reticulin-staining. In the

* The term " small round cell " is used descriptively by some pathologists to cover lymphocytes, plasma cells and fibroblasts seen together in some chronic inflammations. This imprecise bracketing is a confession of idleness: the attempt should be made to identify cells with different functions.

early stages these fibres are easily stretched; later on they tend to contract, and scars become puckered.

The Mechanism of Inflammation

The chemical stimuli which bring about this complicated sequence of events have been under investigation. In every injury, however trivial, which sets up an inflammatory response, there are always a few cells killed. This liberates two substances—

1. HISTAMINE. This is a well-known substance of definite chemical structure and physiological activity. Notable in this connexion here are the activation of smooth muscle, and the increase of capillary permeability. The result of its liberation is vasodilatation and the exudate of serum from the dilated capillaries. The loss of fluid from the blood and stagnation in the widened vessel predisposes to clotting in the vessel (called *thrombosis* in pathology). Histamine is not capable, however, of attracting polymorph leucocytes, and a substance which does so was described by Menkin in 1936 as leucotaxine.

2. LEUCOTAXINE. This is a group of polypeptides rather than a single substance, which are extractable from inflammatory exudates and are not present in normal blood. Leucocytes migrate towards it *in vitro*—a *chemotactic* effect—but it has not the effect on smooth muscle of histamine, nor does it give colour tests for histamine. It also increases capillary permeability. It takes some 30 min. to form, and has been produced by other means from tissues, e.g. by the action of lewisite on the skin, and by peptic digestion of albumen. It is better to regard it as a type rather than a single substance, but it is of importance in showing that the phenomena of inflammation are not merely haphazard adventures of the cells that take part, but are definite responses to the chemical events taking place in inflammation. Other factors in serum have been recently described.

The Varieties of Inflammation

Although the basic events in inflammation are similar throughout, there are many variations in detail and in the proportion of the various events. The named types of inflammation are conveniently considered under two heads: (*a*) variations which are related to the part of the body concerned and, (*b*) variations due to bacterial types, which always produce a special reaction wherever they may be found in the body.

VARIATION IN SITE. Two special locations are deferred until all inflammation can be considered—the bones and joints (p. 106) and the central nervous system (p. 98).

(i) *Surfaces covered by Squamous Epithelium.* The inflammatory exudates find their way as always into any spaces available. They accumulate, therefore, first under the waterproof keratin layer (stratum corneum) which is lifted off by the underlying fluid to give vesicles or bullae. The cellular migrants follow. Thus almost all primary infections of the epidermis, whether chemical irritants externally, bacterial, or substances circulating in the serum which irritate the skin in depth, all alike tend to produce bullous or vesicular inflammation. A second place of accumulation is between the cells of the prickle cell layer (" spongiosis ") which is favoured by the parasitism of these cells by viruses (herpes zoster, chickenpox, smallpox) but also occurs in those inflammations of the skin arising from internal substances to which the patient's skin is sensitive, called eczema by dermatologists. Thirdly, in a group of serious but rare dermal diseases the plane of the fluid accumulations may be next to (either above or below) the basal layer: the reason for this is not known.

In the dermis, the inflammatory responses are more standard and the occurrence of the inflammatory cells around the blood-vessels is what would be expected from their source, and the perivascular residence of the normal resting macrophages.

Increased epidermal growth is commonly a part of the process. When the inflammation is due to friction or pressure, there is thickening of the keratin (e.g. the common corn, or hard patches on the hands of the manual labourer). When the inflammation is bacterial or due to fungus, the growth process of the skin leads to a natural cure by exfoliation.

(ii) *Surfaces covered by Mucus-secreting Epithelium.* The gut, nasal and respiratory cavities. The rapidity and direction of growth, in the intestine at any rate, is quite different from that of the skin; the growing cells at the bottom of the crypts slide upwards on the stroma to desquamate from the top of the villi. In animals this process may occupy only 24 hr. In addition to this, the capacity for outpouring of mucus and so mechanically washing itself free from organisms is important, quite apart from any anti-bacterial action of the mucus itself. The part played by cilia has been alluded to (p. 8), and the grosser movements of coughing and peristalsis play a very important part where they occur.

In general then the type of inflammation here is *catarrhal*, characterized as in the common cold by copious fluid output, so copious that in the severe bacillary dysenteries and cholera the patient may dehydrate himself to death. The mucus output is shown to be controlled, at least in part, by direct responses of the mucosa to

mechanical or chemical irritation, though possibly also by nerves. After this phase the ordinary purulent phases follow, but in the gut with its thin cellular surface desquamation and ulceration, with bleeding, and sometimes membrane formation may be found.

(iii) *Surfaces covered by Endothelium.* Endothelial cells are mesodermal cells modified to enable opposing surfaces to glide on each other in movement, a lubrication effected by the secretion of a fluid containing hyaluronic acid. In inflammation they may swell up and become more prominent for a while, but they take no active part in phagocytosis and are swiftly obliterated in the rest of the inflammatory exudate and macrophages that find the thin serosa no obstacle. A fibrino-purulent inflammation of a serous membrane is therefore a straightforward textbook reaction in the early stages. The great surface of these membranes and the capacity of the cavities they line permit the accumulation of a culture of organisms in protein-containing exudates and an absorption of toxins that makes general peritonitis or pleurisy clinically dangerous.

In the repair phases, the trouble is that the fibrous tissue organizing the exudate crosses the space. Where this occurs with short adhesions so that the two membranes, visceral and parietal, are fused, as in the pleura, it may matter little to the patient; but in the abdomen the presence of long fibrous bands, owing to the stretching of young fibrous tissue by widely travelling coils of gut, carries with it dangers of strangling the mesenteries and causing intestinal obstruction. The occurrence of fibrosis of any sort in the female pelvis is a threat to migration of the ovum and so to normal pregnancy, and in the anterior chamber of the eye organization of bleeding will be followed by adhesions that obstruct the flow of the aqueous humour. Perfect resolution is therefore the aim in these situations, achieved by removal of massive intra-abdominal bleeding surgically, and by prolonged complete rest in the eye; the patient's movements disseminate the fibre-forming cells better than their own unaided efforts.

The Lungs. It can be demonstrated that the cells lining the lung alveoli, like those of the serosae, are not phagocytic, and though they may desquamate and become difficult to distinguish histologically from the macrophages of the lung, they are a different series of cells. The inflammatory exudate will accumulate in the alveolar cavities, in those of the bronchi and in the pleurae if there is contact between the inflamed part of lung and the pleura. The processes of inflammation are little modified but because of the importance of lung infections clinically their causes and consequences require fuller treatment.

The Pneumonias. In considering the inflammations of organs not openly exposed to the bacteria of the outer world, the routes of access are the first things to consider. In general, carriage of organisms by wounds, by direct spread from adjacent infected foci, by the blood-stream, and by natural passages fall to be considered, but in the lungs the last is the only one of great significance.

The defences of the respiratory tract against invasion have been already mentioned; before any infection can be established in the lung, derangement of ciliary activity and of coughing are essential. If they are out of action, the macrophages will be overwhelmed by the mass of the infection, though they are capable of dealing with the small numbers that slip past the other defence. In the two common types of pneumonia these derangements are well shown.

The commoner is known as *broncho-pneumonia,* an acute purulent infection centred on the bronchi and spreading out from the smaller bronchioles into the adjacent alveoli in numerous scattered foci which take some time to become fused. This is always demonstrably a secondary event, following conditions which depress (*a*) *coughing,* e.g. the extremes of age, painful respiration from abdominal wounds; anaesthetics and sedatives; coma arising from any cause; (*b*) *swallowing,* which is essential to clear the upper laryngeal orifice of mucus and saliva, e.g. dysphagia from obstructive growths of the oesophagus or paralysis of lower cranial nerves; (*c*) *ciliary action,* e.g. volatile anaesthetics, especially ether; the virus diseases measles and influenza; the bacterial disease whooping cough in which the *Haemophilus* colonizes the cilia; blockage of the bronchi; (*d*) which provide an *unusual mass of infective material* inhaled, e.g. sepsis of any sort in the upper air passages, including ulcerated growths; or (*e*) which provide an unusual *culture medium* in the usually dry lung alveoli, e.g. *oedema of the lung.* The bacterial invaders are quite non-specific, any inhabitant of the mouth or pharynx being found, and since the patients are already seriously ill, the inflammatory response may be slight—the terminal " hypostatic pneumonias " of old age. The disease is more a manner of dying than a cause of death.

The less common is *lobar pneumonia* in which as the name implies the area affected is a lobe rather than widely distributed small peribronchial alveoli. The infection is due to a specific group of bacteria known as *Pneumococci,* some of which are common inhabitants of the throat. The explanation of how these establish themselves turns again on the evasion of the two guards by bronchial blockage. Experimental infection is successful with these organisms only if they are injected intra-tracheally or in a plug of mucus pushed into the bronchioles by catheter, which give the pneumococci just

that initial start which they require. In man, the early stages of the inflammation are hard to study; the frequency with which the illness struck a healthy man abruptly (so-called primary pneumonia) was partly explained by transient strains, in particular exposure to cold weather; in these cases partial reflex collapse of segments of the lung is known to occur, and these might provide the necessary focus, as might a mucus plug in a smaller bronchus. From such a focus the infection spreads in the lung as a classical purulent inflammation; the exudate collects in the available spaces, the alveoli, and respiratory movements and this exudate carries the infection through the whole lobe with great rapidity, so that within 48 hr. the lobe is consolidated by an early fibrinous exudate in all alveoli—red, solid, friable (known for years as "red hepatization," from the alleged resemblance of the solid organ to liver). As the polymorph and macrophage stages advance, the lung becomes grey, the pulmonary circulation through it shuts down (grey hepatization) though the bronchial arteries keep it alive and maintain the inflammatory response to the next healing stage, when the grey tissues becomes yellow and softened; this is the stage of recovery, and the pus is coughed up. If the lung is examined some time after the attack, the structure will be found to have regained the normal; that it is not physiologically so perfect is shown by an increased risk of recurrence.

In both these forms of pneumonia, the inflammation spreads to the pleural surfaces as a fibrinous exudate—a matt instead of the usual shiny surface is the first indication of this—which may increase in amount and contain the causative organisms. This filling of the pleural cavity with pus is known as *empyema thoracis* (pus-filled maxillary antra and gall-bladders are also called empyema).

Lung abscesses result (*a*) from inhalation of one or a few large septic fragments under the same conditions that produce bronchopneumonia; the two conditions converge. The localization of these inhalation or bronchogenic abscesses is characteristically in the axillary segment of the upper lobe or the apical segment of the lower lobe of the right lung, as was shown by Brock to follow anatomical principles in the distribution of the openings of the bronchi and the posture of the patient in bed. (*b*) The second type of lung abscess, the pyaemic, comes from infected thrombus carried by the systemic veins to the lung; these are more often multiple and have no favoured position, but tend to be peripheral.

Two further effects of inhalation merit brief mention; *lipoid pneumonia* from the inhalation of liquid paraffin or animal (hydrolysable) fat such as milk or cod-liver oil, by patients with dysphagia (infants, sufferers from chronic nervous disease); this brings about a

macrophage exudate, and a plasma-cell exudate probably of similar origin is described in infants. *Acid digestion* converts the lung into a slimy evil-smelling solid black mass when gastric contents are inhaled shortly before death in patients with severe vomiting, or even as a post-mortem event during transport of the body; the appearance may prove puzzling and be thought to be a form of broncho-pneumonia.

Other Solid Organs. There is little modification of the inflammatory process. The healing of wounds of internal organs follows the same course as healing of those of the skin, but regeneration in the area of scar tissue does not occur; instead, compensatory overgrowth of uninvolved parts of the organ is usual.

The first point about infected inflammation is the route of access of the organism. Direct wounds in warfare or road accidents may set up abscesses in any tissue of the body, but in ordinary life three sources are to be considered: spread from adjacent infected focus; spread by the blood-stream; spread by a natural passage when such exists. It follows that inflammation in a small organ with no duct is a rare event, e.g. thyroiditis.

Blood-borne inflammation occurring in pyaemia is common; the organs affected depend on the vein involved by the infected thrombus; if it is a systemic vein the pyaemic abscesses will be found in the lung; if it is portal, in the liver; if the pulmonary venules are, as so often, eventually involved by the growth of the organisms in a pulmonary pyaemia, or if the thrombus is on a heart valve, the pyaemic abscesses may be distributed anywhere by the arterial blood-stream. The distribution of the pyaemic abscesses is more or less random.

By contrast, when the infection spreads up a duct, the abscesses resulting are often grouped along one part of the duct system or confined to one duct. It will be seen too that for this retrograde spread up a duct to occur, it is almost essential for the duct current to be stagnant.

Variation in Inflammation due to Bacterial Types

Apart from the quantitative variation due to the virulence or number of any particular micro-organism, or the resistance or feebleness of the host, there are striking variations in the quality of the inflammation produced by types of bacteria, these qualitative differences being repeated in whatever host or whatever organ of the host they may be found. Sometimes the particular character of the inflammation depends on known factors in the bacteria, more often at present we can only record it as a curious fact in the disease.

There is a group of organisms so important in themselves and so different from the foregoing in their reaction that they must be taken separately—such are the tuberculosis bacillus and the organisms that cause syphilis, malaria and amoebiasis, and the viruses. Again, some inflammatory responses are so unusual that they too must be postponed. The variations in the ordinary inflammatory response that follow are all determined by the character of the organism, but all fall in the pattern of an acute inflammation.

SEROUS INFLAMMATION. In this the inflammatory exudate is poor in fibrin; in consequence the inflammation tends to spread readily. This may be due to poor resistance—in the streptococcal inflammation of the placental site in recently delivered mothers, for example, a serous parametritis was found in the connective tissue lateral to the uterus. It may also be due to the streptococci themselves, for they have the power to form a *fibrinolysin* and a *hyaluronidase*, the one breaking down fibrin as fast as it is formed by the body, the other dissolving the polysaccharide cement that holds the connective tissues together. Streptococcal infections thus tend to be diffusely spreading (cellulitis, erysipelas).

FIBRINO-PURULENT inflammation on the contrary has an excess of fibrin, the type example being that due to the *Staphylococcus pyogenes* which elaborates a *coagulase* that produces the coagulation of plasma *in vitro*.

The term *phlegmonous* is an old one used to describe an inflammation of the wall of the alimentary tract usually due to streptococci and of an intermediate sero-fibrinous character.

HAEMORRHAGIC INFLAMMATION explains itself; in anthrax, in any organ (lung, skin) a great outpouring of oedema fluid and red cells is found added on to the other happenings in inflammation. Plague and haemorrhagic smallpox are similarly attended.

MEMBRANOUS is the term used when a fibrino-purulent exudate incorporates a dead epithelium, so forming a thick leathery slough which remains adherent until dissolved after about a week by the polymorph and macrophage reaction below it. Such an inflammation occurs in *diphtheria* (from the Greek word for a membrane). The membrane, unlike an inflammatory exudate, cannot be dislodged by swabbing, a point of value in diagnosis of diphtheria from streptococcal tonsillitis.

TOXIN PRODUCTION is again well exemplified by diphtheria, which liberates into the blood-stream a powerful toxin; the latter acts on the cytochrome system of many cells, especially those of cardiac muscle and the nervous system. The organism of diphtheria has no invasive power at all, and is confined to the extreme surface of its

membrane, whether this is formed in the common site, the throat, or on a wound surface or the conjunctiva.

Another excellent example of toxin production is the group of anaerobic bacteria found in cultivated soil, those of *tetanus* and *gas gangrene*. In both of these the inflammatory response is very slight; tetanus toxin, carried along motor nerves to the spinal cord from an infected wound or scratch which may be almost unnoticed, acts specifically on transmission across synapses so that violent reflex spasms prevent breathing and kill the patient by exhaustion; if the patient can be kept alive, however, the neurones will detoxicate themselves without permanent damage.

In gas gangrene, the plethora of toxins available has been alluded to already. The most surprising feature of this infection is the complete paralysis of the ordinary inflammatory response even to swarms of bacteria and extensive necrosis of tissue (especially muscle); practically no polymorphs can be found. The fatal outcome is not surprising.

If an organism produces neither toxin nor inflammatory reaction we probably know nothing about it: there is no illness.

NECROSIS without inflammatory response is also found in *amoebiasis*, an infection of the colon by a parasitic protozoon (p. 82).

A MACROPHAGE RESPONSE without any polymorph exudate is the reaction to the *typhoid group* of bacteria. These are swallowed in polluted water and absorbed mainly by macrophages in the Peyer's patches of the gut and the draining lymph glands, marrow, spleen and liver. The macrophages in the immune patient kill the organisms; in a susceptible one, the organisms multiply and kill the macrophages, recolonizing the blood-stream. The Peyer's patches, swollen by the inflammation, become prominent, and ulcerate, so discharging the bacteria in the slough back into the gut. Typhoid is not a primary inflammation of the mucosa, and so does not produce catarrhal inflammation; the inflamed bowel is usually sluggish rather than overactive. With the separation of the sloughs severe bleeding or perforation of the bowel may occur, about three weeks from the onset of symptoms; if this discharge of organisms is successfully managed the patient will recover, because by this time antibody formation in the serum will clump and immobilize bacteria so that they can be successfully phagocytosed. Local colonies may, however, establish themselves in gall-bladder or bones and persist for many years, often without causing further illness ("carrier state"). The ulcerated areas of gut formed by separation of the sloughs heal without scarring. The disease forms a contrast with

genuine inflammation of the bowel in the dysenteries, both acute and chronic.

Inflammation due to Viruses

These pathogens have two particular points of difference from the bacteria, one their size, below what is visible in the wavelength of visible light, the other their delicacy which may make it impossible to cultivate them except actually in living cells (in the intact animal, in tissue cultures or on the allantoic membrane of the hen's egg). The details of their morphology are dealt with in the volume in this series on Bacteriology.

Their invisibility is sometimes compensated for by the formation of inclusion bodies, or colonies of virus in the cells which are easily seen. In the absence of such, the only proof of infection by a virus lies in the passage of the infection through a series of animals. It is often tempting when no infective organism can be seen to suggest that a virus is present, and it should certainly be looked for, but the mere absence of visible organisms in the presence of an apparently inflammatory histology is not evidence of virus aetiology.

Two things follow from their delicacy; they are likely to be intra-cellular parasites, using the mechanisms of the cell to make up for their own deficiencies, and so they are much more likely to be specialized; secondly, lurking in dust for accidental opportunities to infect a passer-by is less easy than for the coarser bacteria, and close contact of cases or an insect vector is therefore usual. In fact, the infectivity of some virus diseases was known hundreds of years before viruses were discovered.

Intra-cellular parasitism is not unknown in bacteria, but is uncommon and usually affects phagocytes (leprosy bacilli, Plate 4, are a good example). Close contact with the cell cilia is essential for the delicate organism that causes whooping-cough. In viruses, the cell membrane must be involved before the inside of the cell can be infected, and adsorption to the cell membrane has been shown in several groups by Burnet. The enzymic mechanism by which penetration is successful is not yet clear. Once inside, the cell is affected in several ways—

(i) NOT AT ALL. Non-pathogenic viruses as regular inhabitants of cells, notably those of the throat lymphoid tissue and intestine, have been demonstrated frequently since the tissue-culture techniques of virus study have been elaborated in the past ten years.

(ii) DYSFUNCTION; the group of viruses found in vesicular eruptions of the skin (e.g. smallpox, chicken-pox, zoster, herpes febrilis)

all bring about irregular formation of the prickle-cell layer and the keratin over it (acantholysis), sometimes after previous proliferation.

(iii) PROLIFERATION with faulty keratinization is found in *molluscum contagiosum*, and with normal keratin in the common wart; this result, growth of the cell in an unusual manner following its colonization by virus, has led people to look for viruses in cancerous growth (see p. 250).

(iv) DEGENERATION of specialized structures in the cell, best exemplified by the breakdown of the Nissl substance in neurones infected with the virus of anterior poliomyelitis (Plate 9).

(v) DEATH OF THE CELL (*necrosis*); the hepatic cells in yellow fever, and the most damaged cells by any virus.

In some cases the cells colonized show *inclusion bodies*—the Negri bodies in rabies, the Paschen and Guarnieri bodies in smallpox, the Councilman bodies in yellow fever, and the molluscum bodies in molluscum contagiosum; in most of the others they are absent. Inclusion bodies are rarely seen except in virus infection, and their presence is therefore presumptive evidence of such, but it is not conclusive evidence; and it does not prove that the virus causes the disease.

The inflammatory reaction to the presence of the virus itself may be slight. Lymphocytic infiltration and macrophages are commoner than polymorphs except in the presence of dead tissue or secondary infection, when an ordinary inflammation may be added. The frequency with which viruses and lymphocytes can be shown in association has led some to suggest that they act as carriers, and some viruses (vaccinia) have been demonstrated on lymphocytes.

Apart from the damage done to the cells colonized, which may be fatal, an important sequel is that the virus paves the way for secondary infection, e.g. the purulent rhinitis that follows the commonest of all virus infections, the common cold: the infection of the skin lesions that causes the " secondary fever " of smallpox; the bronchopneumonia that follows virus infections of the lung—measles, influenza, and psittacosis (or ornithosis).

RICKETTSIAE are slightly larger organisms (just visible) with an intra-cellular habitat. The best-known are those of the *typhus* group of fevers; they live in capillary endothelial cells which swell and block the lumen enough to bring about small thrombi and haemorrhages; hence these diseases are associated with petechial haemorrhages: " spotted fevers." Another, *Rickettsia burneti*, is the cause of a mononuclear pneumonia in the lung, known also as *Q*-fever, virus pneumonia, or primary atypical pneumonia. This is rarely fatal, but

a mononuclear exudate into the alveoli of the affected patch of the lung has been seen; there is slight cough and fever, and an X-ray shadow which resembles those of early tuberculosis, which is important in the differential diagnosis; this is made easier by the presence of agglutinins in the patient's blood which act on sheep's red cells in the cold, presumably because of a common antigenic configuration in virus and cell. There is again a tendency to secondary infection, and sometimes fibrosis of the lung as a sequel.

One further difference from bacterial disease is the frequency and speed with which viruses change their character; non-pathogens become pathogenic, and well-established virus diseases disappear (cf. p. 105). This happens also in bacterial disease, but much more gradually and slowly and so is less dramatic—centuries rather than decades.

REFERENCES

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See also references in the companion volume to this on Bacteriology for particular organisms.

CHAPTER 4

ABNORMAL INFLAMMATION

THE title of this chapter is in itself unusual, but it is meant to suggest that the process of acute inflammation, which is commonplace in life, is one which is successful in general in stopping and repairing damage from injuries of many common sorts. The evolution of some such mechanism would be essential to free life in this world. But in a number of cases the process of inflammation is by no means so successful; the reason for this difference can sometimes be made out. It may be bacterial; there are certain groups of organisms to which no effective reply is made, and the patient dies after an illness which may be fulminating or protracted; it may be due to factors in the individual patient. But these are the exceptional results of inflammation, though their very inadequacy means that it is in this group above all that the patient requires medical aid. The conditions seen are common in hospital, and perhaps more interesting to the doctor than those in which nature unaided is successful by the process of acute inflammation. The subject divides into—

1. CHRONIC INFLAMMATION (pp. 53-89). The difference is not only one of time; indeed no clear separation exists on this score between acute, subacute and chronic inflammation, which shade into each other. The main difference is that chronic inflammation is not successful; the cause of this failure of the inflammatory process is often a factor which is increased by the inflammatory process, and so will become increasingly effective in prolonging the inflammation the longer it goes on. If you, as a doctor, are to interfere successfully with this vicious circle, you will have to do something about the cause of the chronicity.

The causes of chronicity can be sub-divided into: (*a*) bacterial, and (*b*) non-bacterial or anatomical.

2. ALLERGIC INFLAMMATION (pp. 89-97). Here the difference lies in the patient. In this group the reaction to the inflammatory agent is modified, in the direction of greater severity, by personal variations which may be due to inheritance or may be due to previous contact with the agent. The common example of individ-

uals who are sensitive to pollen and develop hay fever illustrates the point, that this type of reaction is one in which agents that have a trivial or normal effect on most people bring about unusual responses in the allergic.

CHRONIC INFLAMMATION DUE TO BACTERIAL CAUSES

Here the chronicity is seen whenever the invading organism of these types is present, irrespective of the site of the inflammation or the individual concerned.

The inflammation may be histologically more or less specific to the organism; the major diseases *tuberculosis* (p. 61) and *syphilis* (p. 75) are among these. Sometimes the inflammation is purulent in character; the best current example is *actinomycosis*, due to a fungus rather than a bacterium, which invariably produces a picture of multiple abscesses in dense fibrous tissue, in its three favoured sites of the jaw, appendix area, and lung. These indurated masses honeycombed with purulent cavities pass through any tissue, ignoring fascial barriers, and produce multiple sinuses through the skin; histologically composed of chronic purulent inflammatory tissue around the abscesses, they are almost diagnostic in themselves, but usually contain a few recognizable colonies of the organism (" sulphur granules ").

On the whole the rarest cause of chronicity is an evenly drawn battle between the body and the invaders; most so-called chronic infections are in fact recurrent or relapsing. This is true of tuberculosis and syphilis; an example of a long-drawn smouldering infection is given by brucellosis. Sometimes an additional source of difficulty is the clinical labelling of post-inflammatory fibrosis as chronic but none the less active infection. However, without quibbling, the very important diseases tuberculosis, syphilis and their allies are best treated as special cases in this section of infections which are chronic because of the characters of the organisms concerned.

A second reason for chronicity in this group is persistent reinfection from within or without the body (e.g. uncovered or neglected skin wounds or abrasions).

CHRONIC INFLAMMATION DUE TO NON-BACTERIAL CAUSES—ANATOMICAL

Interference with the process of acute inflammation by any or all of the following four causes may make an infection chronic—

1. Poor blood supply.
2. Inadequate drainage of pus.

3. Alterations in normal anatomical structure—fibrosis, degenerations, new growths.
4. Foreign bodies.

POOR BLOOD SUPPLY. The importance of the blood supply is obvious from the account of acute inflammation, and dominates the question of slow healing of wounds or fractures. Incisions in the young heal more quickly and certainly than those in the old, and if this is held to be due to age-changes in the cells of the old, exactly the same difference will be seen in an individual if the healing of facial wounds is compared with the healing of those in the leg. The persistent ulceration of the lower limb in varicose ulcers is bound up in the first place with the surrounding sodden area bathed in venous blood, and with the fibrosis that follows the first attempts to deal with the inflammation; this fibrosis itself curtails the blood supply.

As the inflammation spreads to the arteries and veins of the part, it excites a low-grade inflammatory response in the intima (endarteritis, endophlebitis) which with added blood clot (thrombus) is a most important factor in reducing the blood supply to the active areas of the inflammation.

Other examples will be given below.

INADEQUATE DRAINAGE. One of the commonest and most important causes of chronicity. It is not strictly necessary to remove pus from the body, because in time many abscesses become encapsulated and quiescent in internal organs where drainage is impossible; but until this occurs the patient will have an enlarging septic focus with all its dangers of spread and toxicity; the encapsulation cannot be relied on to occur, and will usually not occur if there is partial drainage. Encapsulation does not necessarily mean that the organisms die out.

The natural route of drainage may be: (*a*) non-existent, e.g. abscesses in brain; (*b*) too high above the floor of the cavity, e.g. the maxillary antrum; ciliary action will keep this cavity empty of mucus but will not drain pus; (*c*) too small for thick pus to flow out of, e.g. the Fallopian tube and many surgical incisions, particularly those made under local freezing, or those made by laymen without any anaesthesia (an additional source of trouble in this group is that the layman will not usually have enough patience to wait till the pus is fluid enough to flow through any sort of opening); (*d*) sealed off early by the processes of fibrinous exudation—again the Fallopian tube, with its narrow uterine end and the fimbriae curled round the ovary (chronic salpingitis; pyosalpinx).

The drainage may be naturally successful but inadequate because communicating cavities are undrained—the urethra will drain and clear up the acute phase of gonorrhoea but the small para-urethral glands and prostate will hold the infection. But in passages which have stagnation, the passage is almost certain to become infected. This rule is well seen in the bronchi and the ureter.

Special cases of undrained cavities are those left after surgical removal of a major viscus, and amputation flaps where drainage is essential; and cases where in spite of drainage the cavity wall cannot collapse, either because it is made of bone or because it has become fibrous (gall-bladder) as a result of inflammation. This last point brings in the third group below.

ALTERATIONS IN ANATOMICAL STRUCTURE. Post-inflammatory fibrosis is one of the more important examples; changes in blood supply have been alluded to before. Changes in epithelial type as a result of inflammation should be mentioned; the replacement of ciliated epithelium in chronic bronchial inflammation by stratified squamous epithelium adds to the physical toughness of the bronchial wall, but reduces its physiological efficiency for cleansing itself by mucus secretion and ciliary action—a change termed metaplasia.

THE PRESENCE OF A FOREIGN BODY may be responsible for keeping up the inflammation, e.g. surgical sutures, missiles (particularly the infected secondary missiles such as stones or pieces of clothing—the heat of explosion usually sterilizes the shell fragments themselves), calculi, dead bone, displaced tissues. Removal of such materials is therefore desirable, and this is particularly the case when they are either contaminated with bacteria or afford particularly favourable lodgement to bacteria, such as masses of dead tissue or fragments of bone in which the crevices form sites for bacterial colonies.

It will be seen that anti-bacterial measures are not likely to prove more than temporarily successful in this group; persistence of a few organisms will be enough to re-colonize the area as soon as the drug is stopped, and there is the great risk of the emergence of insensitive strains (see Bacteriology). If on the other hand the anatomical abnormality is remedied, the process of inflammation may revert to the more effective acute type. But it is essential that this should happen early before there is much fibrosis; once this distortion of tissue is established there is less likelihood of resolution.

Results of Chronic Inflammations of the Above Types

The picture is usually a confused mixture of the stages of acute inflammation, with much pus in some areas and a great deal of

fibrosis in others. Sinuses (i.e. narrow channels between surfaces and underlying abscess or other cavities) discharging pus, and fistulae between viscera, are common. Apart from the cells of acute inflammation, two variants of the macrophage are usually conspicuous: the *plasma cell* and the *foam cell*; the relation of the plasma cell to antibody formation has been mentioned, and these cells are, therefore, most conspicuous when the inflammation is due to an agent which is a strong antigen. The giant-cell type of macrophage is found in particular around foreign bodies. Lymphocytes and fibrous tissue occur in the outer part of the area; endarteritis and endophlebitis are regularly present.

Where there are epithelia, two events may be seen. The healing of the surface is impaired because of the poor blood supply, fibrosis, and active purulent stages below, so that chronic ulceration is found, and the surface covered with a purulent slough under which is granulation tissue of varying vascularity; and secondly, the epithelium may change to a less delicate type—ciliated mucus-secreting or transitional epithelia becoming thickened and keratinized like skin. This change is termed *metaplasia*. Below are some important clinical examples of chronic non-specific purulent inflammation illustrating these points.

BRONCHIECTASIS. Persisting bronchial infection with dilatation of the bronchi and spread of the inflammation into the partially collapsed surrounding lung is seen following any condition which obstructs normal bronchial drainage by ciliary action and coughing. The condition may be (*a*) localized to a sector of the lung, the block being due to new growths or to inhaled foreign bodies, or (*b*) more symmetrically affecting the lower lobes on both sides, together with the lingula on the left and the middle lobe on the right. These massive bilateral cases usually follow a childhood illness in which collapse has occurred, particularly measles and whooping-cough. The inflammation spreading through the lung is accompanied by fibrosis which may extend to the parietal pleura. Once the condition is established, the bronchi become dilated from a combination of inflammatory weakening of the walls, chronic coughing, and fibrosis; the collapse of these cavities if temporarily drained is impossible, the erect posture makes drainage by gravity impossible, and the alterations to the inflamed mucosae and the presence of pus impairs ciliary drainage; the frequent change by metaplasia of ciliated epithelium to squamous does away with cilia altogether. The bacteria concerned in this stage are non-specific and often include some saprophytic members responsible for the offensive sputum; the chronicity of the disease is not dependent on the

organisms, but on anatomical causes, and sterilization of the cavities by antibiotics is of temporary value only, e.g. pre-operatively.

CHRONIC PEPTIC ULCER. This common present-day illness is very difficult to explain. Acute ulceration of the stomach is common enough but heals rapidly, and occurs in areas of the stomach not involved by the chronic disease; these areas are the lesser curve and about an inch on each side of it on the anterior and posterior surfaces of the stomach; the first part of the duodenum; the neighbourhood of surgical anastomoses with the jejunum, either in the experimental animal or in the operation of gastro-enterostomy performed in the past for ulceration; and in a rare development anomaly when peptic mucosa is present in a Meckel's diverticulum. From this list it will be clear that access to acid gastric juice is one likely factor in peptic ulceration, and one step necessary in the cure is to reduce the exposure to this juice. But it cannot be the only factor, since it is a common observation that the suture lines in these stomachs usually heal perfectly after operation, though they may be within an inch of an ulcer that has been present for years, and are exposed to the same juice.

The histology of these ulcers gives some help in showing why the established ulcer may be slow to heal, though it gives little help in deciding why the ulcer develops at first. In the fully developed ulcer, the inflammation is non-specific chronic purulent in type; the floor is covered by partially digested granulation tissue, often with attempts at epithelial growth at the edge. The base is always formed of dense fibrous tissue, and in this the blood-vessels will frequently be seen to be occluded by thrombosis or endarteritis. This will clearly be a bar to healing, just as it is in other chronic ulcerations. The dense fibrosis will impede the action of the muscular coat in pulling the two edges of the ulcer together.

Although acidity in the gastric juice is necessary before ulcers can develop, it need not be high; it is more frequently high in duodenal ulcers. The reason why a local area in the stomach suddenly becomes ulcerated, while the area an inch away is unhurt, is still elusive; it has been suggested that a small blood-vessel becomes occluded by spasm or thombosis, but because of the wide anastomosis in the submucosa it must be a terminal branch supplying a few glands only, and there is no explanation here why this small hole does not heal like any other acute ulcer. Variations in the gastric juice and motility following psychic and other strains are likely enough, but do not explain why only one small patch of the stomach wall suffers. A mechanical origin for the ulcer is possible; even the common aspirin tablet can be seen by gastroscope to lie

in an acute ulcer on the mucosa. It is possible that the interference comes on the healing side of what starts off as a simple traumatic ulcer that heals in the ordinary man without trouble. A new pathology of the stomach is being built up by gastroscopic observation and we may hope that such studies of the living may clear up this important disease.

CHRONIC CHOLECYSTITIS. The narrow cystic duct, with the spiral valve of mucosa, and the position of the opening of this viscus at the uppermost part of it in the upright position make it from the start unlikely that once infected it will drain at all efficiently; the superficial position of the smooth muscle immediately under the mucosa makes it likely that the muscle available to empty the organ, irrespective of its position, will soon be involved in inflammatory fibrosis. The deep glands penetrating the muscle-coat form poorly drained adjacent foci. Later the whole wall becomes rigid from fibrosis and the tendency of inflammations in this organ to persist is easily explained.

The primary infection may be due to the excretion of organisms by the liver; both streptococci and typhoid bacilli have been shown to be so excreted, and it is likely that the motile coliform organisms from the gut will wander into the gall-bladder, though they may not normally be able to establish themselves there. The tendency for stone formation, acting as a nidus for organisms and partly blocking the ducts, assists their establishment; if the stones become calcified and heavy they will ulcerate the wall from pressure alone, and assist bacterial invasion. Both bacteria and the exudates of inflammation may in their turn act as foci for the formation of calculi (p. 157); the chronicity is once again seen to be a self-reinforcing process.

CHRONIC ULCERATIVE COLITIS is a purulent inflammation of the colon with no definite bacteriological background; the reasons for the chronicity are at present unknown. Most specific bacterial inflammations of the bowel mucosa are terminated by catarrhal inflammation and peristalsis (cf. p. 42) but in ulcerative colitis the muscle, involved by the inflammation and possibly by toxins, becomes inert or is thrown into spasm and peristalsis becomes ineffective. It is unusual for an ordinary case of ulcerative colitis to start with a definite bacillary dysentery, though some cases of bacillary dysentery become chronic.

CHRONIC ASEPTIC INFLAMMATION. The only important cause of this is the persistence or recurrent presentation of the infecting material.

Foreign bodies which are themselves sterile such as the plates and screws of orthopaedic surgery and the sterile shell-fragments of

warfare are encapsulated fairly swiftly by fibrous tissue, often with giant-cells grouped around them. Though rarely there is some progressive inflammation, the usual consequence is post-inflammatory fibrosis rather than chronic infection; this is a distinction that is important clinically.

THE PNEUMOKONIOSES. These very important diseases are chronic inflammations due to the continued presence in the lung of substances inhaled and arrested, as much inhaled matter is, by the pulmonary macrophages. Three substances of major importance are known—coal dust (anthracosis), soluble silicon dioxide (silicosis) and asbestosis. The light metals beryllium and aluminium are known offenders met with in industry.

Anthracosis. This is almost universal in town-dwellers, and has been thought in the past to be of little significance. Gough in Cardiff pointed out that though the threshold of illness arising from coal dust was high, the substance was far from innocuous if inhaled in any amount, giving rise to severe obstructive fibrosis of the lungs and death from right heart failure. The carbon particles trapped in the macrophages are carried to the interlobular septa, giving the reticular pattern in the lungs seen at autopsy: to the hilar and paratracheal lymph nodes which may be almost black: and, in smaller quantity, to nodes in the neck, axilla and upper abdomen. In general, however, anthracosis can be considered the cause of death only in special circumstances.

Silicosis. The industries in which this may be acquired are exceedingly various. Any trade working with hard stone may be involved—grinding metal, drilling rock, mining in hard stone, notably in the South Wales coalfield. The exposure is usually of a few years duration and nowadays in many industries protective measures directed to the suppression of dust at the site where it is formed have done away with the disease completely. The problem is still unsolved where dust cannot be so controlled, notably in mining. The points determining whether a dust will cause the disease are first, the solubility of the powder, which must be silicon dioxide; with one exception (asbestos) silicates are harmless; secondly the particle size, which must be under 5μ and, to produce severe disease, under 1μ. This is partly because larger particles do not remain suspended in the air for so long, and partly on account of the increased solubility of the very small particles. Once in the substance of the lung, they excite a peculiarly dense concentric hyaline fibrosis which gradually increases in size and in a few years may fill the lung substance with nodules up to half an inch across. The lung tissue between undergoes a compensatory dilatation of the

alveoli (emphysema) which renders the respiratory exchange inadequate, and imposes a burden on the right side of the heart; a chronic bronchial infection is usually also present, but the most important sequel is the onset of a dangerous form of tuberculosis, with rapid solution of the nodules into cavities. The disease therefore carries not only a very high disability rate but a considerable mortality, and is a major problem in industries where silica dusts cannot be suppressed. No way is at present known of getting the silica out of the lung.

Asbestosis. This is both less common and less dangerous, and is more easily suppressed by factory precautions in the few places where asbestos is handled. The material is magnesium silicate in fibrils, and when these are inhaled they are stored in the lung as asbestos bodies—match-like objects, faintly brown from absorbed iron, and up to 200μ long. These may induce foreign-body giant-cell formation, but also induce a slowly progressive diffuse fibrosis of the lung with the usual compensatory emphysema in the unaffected (usually apical) areas and diffuse pleural fibrosis. Chronic right heart failure thirty or more years after leaving the factory may occur, and asbestosis is a predisposing cause of carcinoma of the lung, though not of tuberculosis. The asbestos bodies may be seen easily in sputum, in smears of lung tissue at necropsy, or in sections.

Berylliosis. This light metal was introduced into industry about 1935; dangerous absorption occurred from handling beryllium phosphors, the coating of the tubes used in strip-lighting. It is an illustration of the potential danger of all unknown industrial materials, being inhaled easily owing to the lightness of the dust, and at first being treated with little respect. It is absorbed by the lungs and stored both there and in liver and lymph-nodes in microscopical foci of macrophages with fibrosis. After a few years it proves fatal from dyspnoea and cardiac failure. Similar nodules occur in the skin in wounds caused by fragments of broken glass from tubes coated with beryllium compounds.

No inhaled substance can be assumed to be harmless until long experience has shown it to be so, and all dusts are hazards to be controlled. Several substances thought only to cause pulmonary fibrosis have been shown to carry an increased risk of cancer—the iron ore known as haematite, and all dusts containing chromates, for example.

Talc granulomas of similar histological structure may be seen from the dust, used in lubricating surgical gloves, finding its way into the peritoneum or open wounds.

CHRONIC INFLAMMATION DUE TO SPECIFIC ORGANISMS

Tuberculosis

By far the most important single member of the group of chronic infections due to specific organisms, tuberculosis is losing ground, in civilized communities, to modern hygiene and drugs, but still remains a most serious disease.

The causative organism *Mycobacterium tuberculosis* is present in every case of the disease in all stages; it can be cultured *in vitro* for a long time and then reproduce the disease when inoculated into a susceptible animal. It thus satisfies Robert Koch's postulates; although they are fulfilled in the case of tuberculosis, it should be noted that they do not prove that the presence of the organism is invariably associated with disease; tubercle bacilli may be present temporarily in healthy subjects, and even in the tuberculous patient from time to time the disease may become quiescent without complete disappearance of the bacillus. The second factor in every bacterial disease is a *susceptible patient* and in no disease is the patient's reaction to the disease more significant than in tubercle.

The descriptive account of the organism and its cultural behaviour will not be repeated from the companion volume on Bacteriology except to recapitulate the following points which are necessary for a discussion of the pathology of the disease—

1. Two types only are pathogenic to the human, the *human* and the *bovine*; they provide some immunity against each other.
2. The organism is slowly growing and non-motile.
3. It contains much lipid, both ester and wax, incorporated in the bacterial substance, and as a result stains in a characteristic way (acid-fast staining, see Bacteriology).
4. It requires oxygen for its growth, i.e. it is an obligatory aerobe.
5. No exo-toxin is demonstrable.

Sources and Routes of Entry

1. Inhalation of airborne organisms, derived ultimately from another case of the disease, but capable of lying dormant for many months in dust, particularly where away from sunlight. These organisms are more frequently of the human strain. Like any other inhaled particulate matter, they may be arrested and removed by the ciliated mucosa of the upper respiratory tract, or carried into the lungs beyond the ciliated bronchi, where they are ingested by

from milk, but dust-borne and milk-borne human organisms are still important. Two main sites of arrest, the tonsil and the lower ileum; the lesion at entry in these sites is microscopic, but may be found in tonsils removed surgically; the organisms are rapidly carried by macrophages into the related glands and the disease may present as cervical or mesenteric gland tuberculosis, or be latent.

3. Accidental or experimental inoculation into the *skin*, occasionally seen in those whose work requires them to handle tuberculous material, or into the *blood-stream*, which as well as providing a convenient method of study in the experimental animal is a regular event in the course of the human disease. The arrest of the bacilli occurs in organs in proportion to their content of macrophages; further development depends on the strain of organism, the animal species, and possibly on oxygenation, at least when it comes to the larger lesions. If bovine bacilli for example are injected into the blood of the rabbit the tubercles develop mainly in lung and kidney; if into the guinea-pig, in the liver and spleen. The disproportionate frequency with which bovine bacilli are found in human bone tuberculosis may be another example of this.

Once these organisms are inside the body, the effects they produce will depend on the natural or acquired resistance of the animal, and on the dose of organisms. There is no extra-cellular destruction by antibodies, but antibodies limit spread and aid phagocytosis. This is carried out by macrophages, after a transient unsuccessful attack by polymorphonuclear leucocytes, which may be present in some numbers but in uncomplicated tuberculosis do not imply a purulent reaction.

The macrophage response is early and highly characteristic, because of the morphology of the macrophages concerned, with ill-defined stellate outlines and pale foamy cytoplasm; these have been known for many years as "epithelioid" from a resemblance to the cells of squamous epithelium, but this is merely a morphological variation of the ordinary phagocyte and not a new or special cell. The character is, however, a most useful one in the microscopical recognition of tuberculosis, as these cells are more easily seen than the bacilli. This phagocytosis is neither rapid nor efficient, for the bacilli live for some time inside the cell and may multiply and kill it; during this phase the motile macrophage lends to the non-motile tubercle bacillus an additional faculty for spreading locally; otherwise dissemination of the bacillus would be dependent on its own slow growth or on the movements of the host. Moreover during this phase the cell protects the bacillus from chemotherapeutic agents given to the patient; some anti-bacterial agents cannot

penetrate the cell at all and even the best does so only late and in great dilution; streptomycin is effective on intra-cellular organisms only in a dose sixteen times that effective on extra-cellular ones. The natural resistance to the disease is therefore imperfect; it is greatly improved by the acquisition of immunity; and with a dose small in proportion to the immunity of the patient the macrophages may well extinguish the bacilli, and there will be no disease.

When macrophage phagocytosis is unsuccessful, tuberculosis becomes a disease. It must be considered under three headings, because the patient's reactions are so much modified by the immunity and hypersensitivity that may follow the first infection that the course of the illness is entirely different. The disease is discussed under the headings: primary tuberculosis; post-primary tuberculosis; and tuberculosis in a hypersensitive subject.

I. Primary Tuberculosis

The infection entering the patient by either the first or second route listed above is not suppressed at once by the macrophages available. In the human this is seen more often in the lung than elsewhere. In the lung, the primary focus is known as the Ghon focus, and consists of an area of tuberculous inflammation in any part of the lung, commonly subpleural; the size may be such that it is easily visible on radiography. But material is more conveniently obtained from the experimental animal which can be killed at any stage in the process that it is wished to follow, and fortunately the histological patterns are comparable to those in the human.

The first step is the accumulation of numbers of epithelioid cells by local multiplication and immigration from the blood-stream; it is usual for some of these to take up giant-cell form by fusion and by nuclear multiplication. These large cells with up to a hundred nuclei are an early and characteristic component of the reaction to tuberculosis, though giant-cells, not so very different to those of tuberculosis, may be found in many other inflammations and the diagnosis of tuberculosis should not be made on giant-cells alone. The name Langhans giant-cell is often given to them; typical examples are seen in Plates 5-6. Around this focus develop delicate fibrous tissue strands, reticulin at first, later collagen, and if the disease is held this zone gradually becomes thicker. Lymphocytes accumulate in the outer zone, but there is none of the vascularity or exudation of purulent inflammation and the absence of blood-vessels is striking, and may be responsible in part for the occurrence of necrosis or *caseation* which results from the effect of the tubercle bacilli on the macrophages and the surrounding tissues. Their

nuclei become faint and the cell outlines disappear; the whole area becomes amorphous, eosinophil and granular—again a feature of tuberculosis which is not seen in purulent inflammation. By this time the lesion is visible to the naked eye as a *miliary tubercle* (from *milium*, a millet seed, referring to the size of the tubercle and not its numbers); it should be regarded as the unit on which diagnosis may be based with its characteristic zonation of epithelioid cells, giant-cells, and maybe caseation in the centre, lymphocytes and fibrous tissue around.

As a natural consequence of the type of inflammation, with no vascular happenings and a cellular reaction dependent on slowly growing cells and not on the accumulation of cells readily and rapidly manufactured by the marrow, a tuberculous inflammation is a slow, cold, painless affair compared with a purulent inflammation. Hence the clinical term " cold abscess "; the description of the softened caseous matter as " tuberculous pus " is not strictly accurate as polymorphs are few, but it is much more convenient and brief than " tuberculous caseous material."

In the histological diagnosis of tubercle, note that in any one tubercle your section may not pass through the part that contains the giant-cell, and that caseation is not an essential part of the lesion and may indeed be quite absent; but in the whole of a section it is most unlikely that you will not find each characteristic feature represented somewhere. Make the tubercle the basis of the diagnosis and not merely one component of it; epithelioid cells can be recognized alone, but only with experience.

The bacilli are on the whole hard to find, though in occasional samples they are numerous; they are more likely to be present in areas where there is a lot of nuclear debris or polymorphs; they may be seen inside cells, including giant-cells, or outside them. But the recognition of the histological pattern is so nearly completely diagnostic that the demonstration of the bacilli may usually be left to special investigations, difficult cases or research projects. The possibility that they may exist in forms which do not take stains has been put forward to explain the large lesions which may be found apparently free of bacilli.

Further events in the established tubercle lead to one of two terminations—complete healing by fibrosis or generalization. The prolonged up-and-down struggle which is seen in later stages is unusual in the primary phase.

1. HEALING BY FIBROSIS WITH CALCIFICATION was the usual method before chemical antibacterial agents were introduced. The wall of fibrous tissue became thicker, and inside it the whole area underwent

caseation; inflammatory cells died out, and the proof of the tuberculous origin was obscured, though bacilli could be found with care. Calcification of the caseous material was so usual an ending that the presence of a calcified nodule in an area where tuberculosis could be a cause was almost certain evidence of past tuberculosis when bacteria had died out and there was no histological evidence of diagnostic value; but other fibrous and necrotic tissue may calcify. The chemical form taken may at first be that of calcium soaps with the fatty acids present in caseous matter, but this alters constitution later to the standard hydroxy-phosphate (apatite) crysta that is the final state of most calcium deposits in the body.

Healing by *resolution* has been seen since the introduction o streptomycin; patients with miliary tuberculosis and meningitis so treated might largely recover from the tuberculosis and die from obstruction to the C.S.F. In their lungs many stages of resolution of miliary tubercles could be made out; the nodules became vascular lymphocytes moved in, and the giant-cell macrophage layer broke up and disappeared. The final fibrous scar was very inconspicuous Whether this was also an occasional event in tuberculosis not so treated is not known. Changes in the healing of lesions under other agents are described from surgical specimens excised nowadays after considerable preliminary therapy.

2. SPREAD. This occurs partly by direct growth, but the slowly multiplying immobile bacilli make it a slow process; there is no exudate to aid the movements of the patient in spreading the organisms about. Foci thus remain discrete much longer, and retain their outlines long after a purulent inflammation would have become confluent. Migrant phagocytes, however, carrying viable bacilli move away from the focus and often die in its vicinity, so that satellite small lesions grouped round the primary one are usual. This process of natural spread often alternates with fibrosis, either in time or at different points round the periphery of the mass. They assist diagnosis, both naked-eye and histological.

3. LINED CHANNELS. Spread directly through the tissues is a slow and unimportant event compared with the spread by lined channels, which are certain to be reached sooner or later in the growth of the tubercle. In primary tuberculosis, the *lymphatic* route is conspicuous, made even more so by the absence of it in most forms (notably the pulmonary form) of post-primary tuberculosis. Not only is it early but it is also massive, and the large lesion in the lymph-nodes is often due to a microscopical or even undiscoverable one at the site of entry. Thus the small primary pulmonary focus after healing—a calcified mass the size of a match-head—may be

most easily located by tracing back from the similar larger healed mass found in the pulmonary lymph-nodes. The histological picture in the node is standard. Both embolism in the lymph and permeation of the lymphatics contribute to this spread.

The *blood-stream route* may be reached in two ways: (*a*) as a massive leak from the ulceration of a big caseous lesion into a vessel, often from a caseous mediastinal gland into any of the veins in that area, or via the thoracic duct; (*b*) as an occasional microscopic leak from a focus of any size anywhere into a small venule. The first leads to a major disaster—generalized haematogenous tuberculosis, often called miliary because the patient did not survive long enough for the lesions to grow any larger; (*b*) is at the back of all forms of what is called surgical or local tuberculosis. These two events may occur from the primary lesion or from post-primary lesions; they are more likely to be serious in the primary, before the resistance of the patient is mature; that (*b*) is a regular event is better shown by the presence of microscopical lesions scattered about in the body of 95 per cent of patients dead after pulmonary tuberculosis. It is only rarely that it then leads to fresh disease; but it implies that an apparently local lesion coming to medical notice in the kidneys or bones or testis has originated in an active, but not necessarily a very active, focus elsewhere in the body, commonly pulmonary. The organs principally affected in the major dissemination are the lungs, kidneys, spleen and liver; cerebral lesions spreading further by the C.S.F. are the source of the fatal meningitis (p. 100) that usually but not always brought the patients to the doctor. In the lesser spread, bones and the genito-urinary tract form two of the main sites. The histological picture in all parts of the body is similar. Other lined channels may in turn be affected.

BRONCHI: an extremely important method of spread in the post-primary pulmonary tuberculosis, and it is not at all uncommon for the primary lesion to disseminate by this route. The bacilli set up new lesions in the lungs and affect the central part of the lungs rather than the subpleural, whereas haematogenous spread is more or less evenly distributed through all parts and some lesions are visible under the pleura. As well as being distributed further into the lungs, the bacilli will be coughed up in the sputum to affect the larynx, tongue, and thence are swallowed and excite tuberculosis in the small intestine. The walls of the bronchi themselves are inflamed and the lumen narrowed.

The cerebro-spinal pathway is the method by which tubercles are disseminated through the meninges (see p. 100). The ureter and the

vas deferens, the uterine tubes and lumen are involved in the spread of urinary and genital tuberculosis.

Rarely surgical implantation may be seen along the track of the aspiration or incision of tuberculous abscesses, but the more common unwanted result is the super-infection of a tuberculous cavity with purulent organisms.

PRIMARY INFECTION in Britain is most commonly seen in childhood, but the response is on the whole similar, though modified by age, in those who are not infected till adult life. This was a very rare thing in urban communities till comparatively recently; old evidence from Germany showed that almost everyone there had received the primary immunizing infection before the age of ten and had either died from it or been rendered immune by it; but with the use of Mantoux testing of the living instead of post-mortem figures to guide us, it appears that present urban conditions allow 25 per cent of people to reach adult life without undergoing tuberculous infection, and this figure is likely to rise. When tuberculosis makes its appearance in unimmunized adults, it is a serious rapid epidemic disease, as is seen when it is carried to the native populations where it is not endemic.

II. Post-primary Tuberculosis

The course of infection in the immunized man or animal is much modified from the above by the limiting value of immunity. A smouldering course with varying acuteness replaces a process that is usually settled one way or the other within months. Lymphatic spread which is prominent in the primary infection is absent, except in tuberculosis of the joints. Generalized, serious and severe infections may still occur, but they are less common and often due to demonstrable " debilitating factors " in the patient in which malnutrition, intercurrent illness, alcoholism, pregnancy, exposure, and possibly psychological strains are numbered.

The difference in the course of these two kinds of tuberculosis, primary (childhood) and post-primary (adult), is one part of the evidence for the existence of immunity as a result of the primary infection. Further evidence comes from the comparison of histological and clinical events in immunized animals; from the rarity of progressive lesions in post-primary disease; and from the non-occurrence of two primary infections in the same individual or animal. A very strong lead was given by the old observations of Marfan in 1898 (sometimes called Marfan's law) to the effect that active pulmonary tuberculosis did not occur in people with scars of severe healed glandular tuberculosis even when they were much

exposed to the risk; the two conditions were common enough to make these human observations of value even within one observer's experience.

The real value of Marfan's observation is the evidence it provides for the possibility of obtaining immunity in the individual by active immunization. This point can be studied in the paragraphs on immunity in tuberculosis in the Bacteriology volume.

The *source* of the post-primary infection lies between (*a*) fresh invasion by bacilli from outside, and (*b*) re-activation of the bacilli responsible for the primary attack. The difference in the site of the two lesions—the primary lesion may be anywhere in the lung, the post-primary is apical or at the apex of the lower lobe, and may be deeper in the lung than the characteristic subpleural Ghon focus: the presence of an apparently unactivated fibrous encapsulated nodule with calcification in the lungs of people dead with pulmonary tuberculosis, either in the middle of or remote from their fatal post-primary infection; and the comparison of the frequency of development of post-primary tuberculosis in those exposed to and those protected from external tuberculosis strongly support the point of view that post-primary infection is re-infection, though some people still hold the opposite view. This does not infer that re-activation of imperfectly controlled tuberculosis cannot occur; it is in fact very important in the long course of post-primary tuberculosis; but it does not account for the lapse of time between the primary and post-primary attack.

SIMON AND ASSMANN FOCI. The post-primary lesions of pulmonary tuberculosis begin very characteristically either in the subapical region of (usually the right) upper lobe (Assmann) or immediately under the apical pleura (Simon). The reason for this localization is unknown, and exactly opposite reasons are given by various authorities. It begins as a nodule of tuberculous infection in the alveoli with accumulation of macrophages and possibly central caseation. As in the primary lesion, healing and spread are both possible, and the spread may occur by the same routes. A critical point occurs when the caseous focus breaks through the fibrous wall to reach a bronchus; three things happen. The first is that the patient now coughs up bacilli; his sputum becomes positive, and he is regarded as an open case and possibly infective to his neighbours. He is also certainly infective to himself, and dissemination along the bronchi will occur; the adjacent areas more heavily infected, but even distant parts of the lung receive air-borne bacilli, and the same process is repeated. Secondly, the discharge of caseous material leaves a cavity in the lung, which can now be seen by

radiography; thirdly, the way is open for secondary purulent infection of the cavity. Fibrosis over the pleural surface in relation to the area is usual and may interfere with treatment by obliterating the pleural cavity or forming adhesions.

The further progress of the disease is one of the greatest possible variety and unpredictability, with healing and quiescence for long periods interrupted by activity. The methods of spread and the methods of healing are similar to those already described; but resolution of an area which is once seriously involved is so improbable that with the present-day safety of thoracic surgery massive resection, exchanging the chronic infection for an assured effective acute aseptic one, is both economical of time and certain, and the loss of the scarred lung negligible.

Two complications are worth special mention. *Haemoptysis* from ulceration of a small pulmonary vessel crossing the cavity is not uncommon as a presenting symptom. Rupture of the cavity into the pleura, often prevented by the usual dense fibrosis, leads to a *tuberculous pyopneumo-thorax* as the cavity is in communication with a bronchus which allows secondary infection of the pleura. This is a grave affair, with a chronic infection developing with two organisms or more in a cavity that is hard to drain effectively and in which persisting foci may be in either the thoracic wall or the distorted lung.

In the long course of the disease, minor blood-stream spread is usual and serious spread occasional. Laryngeal and intestinal tuberculosis are common serious complications; the ulceration of the ileum may be extensive, with diarrhoea. The ulcers have a characteristic appearance with serpiginous undermined edges and granular tissue on the floor; the tendency to spread by lymphatics leads to tubercles visible on the serous surface, and to a tendency for the ulcers to lie transversely across the gut. This complication and the supervention of amyloidosis (p. 122) are as much responsible for the eventual death of the patient as the pulmonary destruction, where damage is also done by secondary purulent infection. The walls of a long-standing cavity may become fibrous and clean from the obliteration of the chronic infection by the more acute in a well-drained cavity; but more frequently the results of purulent infection in the distorted poorly drained lung are to add bronchiectasis to the patient's troubles.

The peak of mortality coming on soon after infection in the young susceptible patient is well known; there is a second peak in mature adult life when the patient may be in a position of responsibility. If the patient passes these, the state of chronic fibroid

PLATE 5. GIANT-CELLS

Giant-cells are easily recognized and often very conspicuous features of histological specimens. They are therefore of considerable diagnostic value but should be considered along with other features and not in isolation. Two sources may be recognized—

1. Inflammatory giant-cells: nuclei may be numerous, but are of normal size. They are derived from macrophages.
2. Tumour giant-cells: nuclei usually few, but themselves of gigantic dimensions and often very darkly stained (hyperchromatic) because of the large amount of chromatin.

(See also Plates 4, 6, and 7 for other examples of inflammatory giant-cells, and Plates 14 and 16 for tumour giant-cells.)
Magnifications × 130–150.

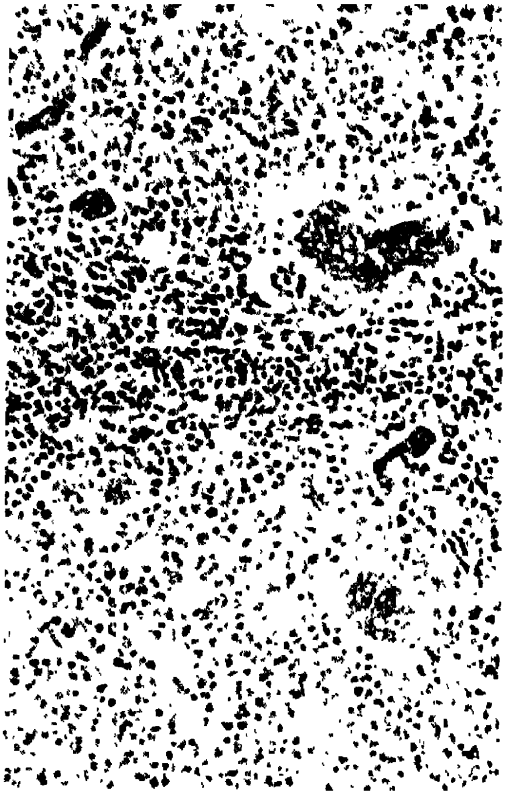
(*a*) Tuberculosis. The " Langhans " giant-cell. Nuclei often in a ring or horseshoe; abundant eosinophil cytoplasm.

(*b*) Measles. The " Warthin-Finkeldey " giant-cell in germinal centres of lymph-nodes, with enormous numbers of packed nuclei—one of the biggest of all giant-cells, but not often seen because measles is such a benign disease that the tissues are rarely examined. These cells emphasize the important part played by lymphatic tissue in virus infections; and the fact that though viruses cannot themselves be seen, some of them may make their presence visible by striking cytological changes.

(*c*) Tumour giant-cells. Primary squamous-celled carcinoma of lung. The very large, very dark nuclei are striking; the size of the cells varies considerably. This cytological abnormality is one example of what is meant by " atypical growth " (p. 215) in malignant neoplasms.

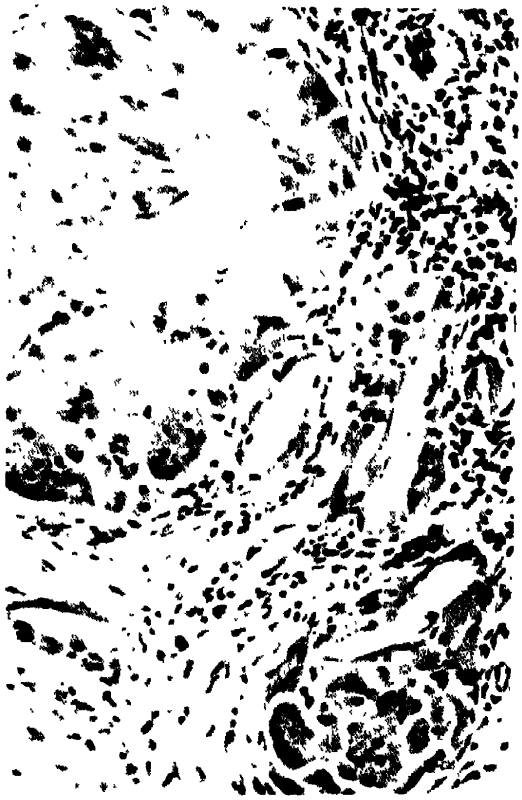
(*d*) Foreign-body giant-cells. Macrophages around the spaces where cholesteride crystals were present (dissolved out in making the section). The macrophages are themselves foamy from ingested lipid. This is commonly seen where squamous epithelium is being broken down in inflammation, or when fatty tissue or cholesterol-containing tissue are involved.

(*a*)



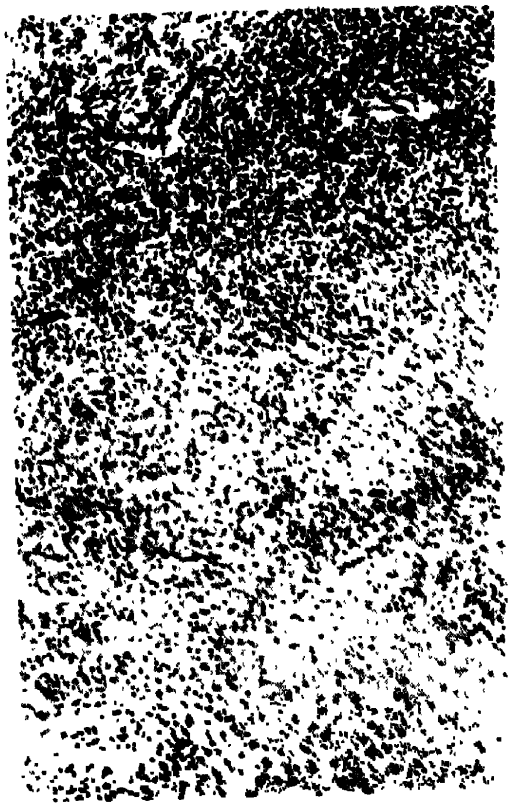
(*b*)

(*c*)



(*d*)

(*a*)



(*b*)

(*c*)

(*d*)

PLATE 6. NECROSIS

Four common examples of massive necrosis of tissue—

(*a*) Tuberculosis. Necrosis of macrophages (" epithelioid " cells) as a result of tubercle toxin. The necrotic tissue is marked by the absence of nuclei and the breakdown of the cells to a fine granular debris, very pale pink with eosin (caseation). Around this are surviving pale-grey macrophages with slightly darker nuclei and black, round lymphocytes. There are satellite tubercles around the main focus, with giant-cells but no caseation. The area of inflammatory reaction is small compared with the area of necrosis. × 80.

(*b*) Syphilitic gumma. The rarest of the four, but the contrast with tubercle is important. The necrosis (bottom right-hand corner) is slight in comparison with the inflammation around it; this is mainly lymphocyte, plasma cell and fibrous tissue; no well-defined epithelioid zone or satellite lesions; giant-cells inconspicuous. × 80.

(*c*) Infarction. Necrosis of a sector of the kidney from anoxia due to arterial occlusion. Coagulation necrosis of the upper two-thirds; the outline of the glomeruli and tubules is clear, but nuclei are lost and the staining is much paler; the subcapsular zone to the left is spared somewhat. There is sharp linear demarcation between normal and dead tissue. Early inflammatory reaction can just be seen in the edge of the healthy part. × 80.

(*d*) Necrosis of a malignant neoplasm. Secondary tubular columnar-celled carcinoma (" adenocarcinoma ") from rectum in the liver; necrosis because it has no proper organized blood-supply to the centre of the growth; the periphery can live on the blood of the normal tissue. The upper right third is necrotic—no nuclei and general loss of structure. In this type of necrosis there is always some trace of " healthy " surrounding growth; well-formed tubules of cells with large nuclei but a general resemblance to rectal mucous glands to the left and below, invading compressed liver columns in the left bottom corner. × 50.

tubercle in the elderly man is often more of a danger to his grandchildren and others than to himself; in tracing the source of infections in patients these elderly people with what are dismissed as slight "smokers' coughs" are very easily overlooked, and in old age unusual variations in tuberculosis may be seen.

III. Tuberculosis during Hypersensitivity

Anyone may develop hypersensitivity to tubercle protein. How this arises is not certain; but it is so often an early consequence of primary infection that it is probably directly related to the antigenic properties of the bacilli in the primary stage. It is recognized clinically by the exaggerated skin response to the intradermal or dermal tests known by the names of Mantoux and others (Bacteriology), and also by the violence with which these patients react to minor doses of bacilli. The same condition may be found in experimental animals. It begins sooner than the immunity which is the other consequence of a primary infection that has healed, and it does not signify an increased immunity but rather the reverse. For these reasons it is probably distinct from immunity, and desensitizing the patient or animal does not decrease the immunity. Although these things cannot be quantitatively measured, if the clinical course of disease is studied in patients soon after, and a long time after, their primary infection, this group of patients who are *hypersensitive but not immune* will be found to react differently from either a primary or post-primary infection. The cause of the sensitivity may be genetic, or racial or a personal idiosyncrasy.

The reaction may be excited in a patient either by a fresh dose of infection from outside or by a blood-stream or other spread in his own body. It is seen only in patients within about a year of the primary infection, and takes the form of an increased and unusually exudative reaction to what may be a number of bacilli so small that there is great difficulty in demonstrating them at all. The best known examples are *tuberculous pleural effusion* and *tuberculous peritonitis*; the curious skin reaction *erythema nodosum* is sometimes due to this bacillus but not exclusively so. In the first two, a massive pleural or ascitic effusion forms, with protein and a few endothelial cells and lymphocytes, from which bacilli may be cultured with difficulty. When pathological examination can be made in the early stages, which is not common as they are benign illnesses, pleural or peritoneal tubercles are found in varying numbers, but with very few organisms; the lesions are full of macrophages and often of polymorphonuclear leucocytes, and there is a great deal of caseation. In none of the other tuberculous assaults on the lungs does this

kind of effusion appear; it is a contrast in every way with the tuberculous empyema referred to above, because it is essentially a benign condition; the fluid is absorbed, with fibrosis (which may be a very serious trouble in the peritoneum because of gut movements, but is immaterial in the pleura). But during the time of the effusion and for about a year later these patients are liable to go down with active progressive tuberculosis if care is not taken. Thereafter their immunity has caught up with their sensitivity and the risks are less.

It is not possible in the available space to touch on the manifold clinical varieties of tuberculosis in the organs of the body; the principles of the source and routes of access of the responsible organism and the histological features of the inflammation are usually characteristic of the foregoing. The skin disease *lupus vulgaris* is a very slowly progressive and benign form of the disease, in which the route of the bacilli is uncertain and the histological picture modified, in that caseation does not occur; there is a course, lasting many years or decades, of progressive ulceration and scarring of the facial skin and subcutaneous structure, leading to destruction of the features.

SARCOIDOSIS. This reaction is histologically closely like that of tuberculosis, and the condition is separable only with difficulty, on the absence of caseation and of adventitious lymphocytes around the foci, which are usually small. As the older name uveo-parotid tuberculosis suggests the lesion is found in the iris and parotid gland; it is frequent in the lymph-nodes, and found in the lungs (causing fibrosis) and bones. Both in the clinical course and in the absence of tubercle bacilli from the lesions it is distinguished from ordinary tuberculosis; the subjects do not develop positive Mantoux reactions, even after inoculation with tuberculous protein. A similar granulomatous picture is found in the histological response to beryllium and in brucella infections; it is possibly best to regard sarcoidosis as a peculiar reaction either to some non-specific substance or in some special individuals to tuberculosis. The many names associated with this disease include Schaumann's benign lymphogranulomatosis, and Boeck's sarcoid.

The peculiar chronic constricting inflammation of the lower ileum and sometimes of the colon known as *Crohn's disease* has enough histological similarity with tuberculosis to be considered here. Some of the cases are indeed tuberculosis, with bacilli demonstable with difficulty, tubercles in the mesenteric glands and a course which includes pulmonary involvement. In the majority the resemblance to tuberculosis is slight—a few giant-cell systems being found among a great deal of chronic non-specific purulent inflammation,

not containing tubercle bacilli, and with only a simple sinus hyperplasia in the glands. These in turn shade off into the more chronic varieties of ulcerative colitis affecting the right half of the colon and the terminal ileum, and until definite aetiological factors are isolated from these chronic inflammations of the bowel precise classification is not possible.

Tuberculous meningitis is discussed later with inflammations of the nervous system (p. 100).

Leprosy

This is a chronic disease with a tissue reaction like that of tuberculosis in many respects; the organism causing it is also an acid-fast bacillus. The organisms are more easily demonstrated in sections from nodular leprosy than almost any other pathogen (Plate 4); in spite of this, they have never been satisfactorily cultivated, either on artificial media or by animal inoculation, and the infectivity of a case is apparently low. The bacillus was one of the earliest described (Hansen, 1874) but its discovery made little difference to the curability of the disease. Even the method of transmission is not known; insect vectors have been postulated, and it has been suggested that it is only infective for children. At any rate prolonged contact appears to be one of the factors concerned.

The organisms are found in the submucosa of the nose, in the subcutis in the nodules, and in lymph-nodes, where they are held in large foamy histiocytes exactly like the epithelioid cells of tuberculosis. The other features of a tuberculous granuloma are scarcely seen; occasional lymphocytes around the lesions and a few small giant-cells may occur.

Two main forms of the disease are observed (*a*) the *nodular* or *lepromatous* type in which there is more or less massive infiltration of the skin of the face and body and lymph-node involvement; organisms easily shown in the skin and nasal mucosa; and (*b*) the *neural* or *maculoanaesthetic leprosy* in which the main lesions are in the peripheral nerves; those in the subcutis may be palpably enlarged. The skin lesions consist of patches in which the colour is altered—usually paler in the dark-skinned races—and skin sensation is lost. Lepra epithelioid cells are found in the nerve-trunks, with a little infiltration, but the bacilli are much harder to find.

Complications include dissemination of the organisms to internal organs in miliary nodules, amyloidosis, trophic changes of which the most peculiar is the atrophy of the bones in the digits by resorption, so that the digits shrink; ulceration of the larynx and eyeball. Death is often from intercurrent tuberculosis.

The disease is not tropical, but its main distribution at the present day is in poorly nourished overcrowded countries, many of which are tropical.

Syphilis and Yaws

These two diseases are caused by spirochaetes that are at least closely related even if the two diseases are not in fact variants. Syphilis (due to *Treponema pallidum*) was first reported in the sailors who returned with Columbus in 1492 from the West Indies where yaws is rampant, and spread as a serious epidemic rapidly throughout Europe. The character of the disease has been much modified by acclimatization between it and the European, but the similarities with yaws are still evident.

The organisms belonging to the genus *Treponema* are fine corkscrew-like threads, highly motile, but delicate and easily killed by desiccation, so that transmission is usually by close case-to-case contact. This is commonly sexual intercourse in ordinary syphilis, but in yaws, and in several syphilitic variants and occasional cases of ordinary syphilis it is not so. The motility of the organism makes it easily recognized while alive by dark-ground illumination, and explains its penetration of intact skin or mucosa and its subsequent dissemination throughout the body.

It is not now a very serious or killing disease, and efficient treatment has reduced its incidence far more effectively than the moral sanctions, secrecy and seclusion of previous generations. Even untreated it carries only about a 25 per cent risk of serious sequels. From 1890-1910 Boeck in Oslo, realizing the inefficiency of the treatment then at his disposal, merely segregated his cases; Gjestland fifty years later was able to trace the fate of about half of these, and found that the incidence of serious tertiary syphilitic lesions was of the order of 20 per cent in men and 10 per cent in women in forty years of life. The phases occurring in some parts of the world (*pinto* in South America, and *bejel* in the Arabs) carry an even lower risk. A positive Wassermann test found in medical examination does not necessarily indicate that there is active syphilis, far less that the things of which the patients complain are due to syphilis.

This quiescence of the spirochaete is seen also in some examples of human congenital syphilis, where there may be numerous spirochaetes without any bodily reaction to them, and in animal syphilis in the rabbit particularly, where virulent human spirochaetes can circulate in numbers with neither reaction of an inflammatory kind nor structural damage.

Syphilis

The descriptive stages are (*a*) *the primary lesion* of entry of the spirochaete. This is commonly on the genitalia, but it may be hidden internally on the cervix uteri; it may be found elsewhere on the skin where it is easily mis-diagnosed; or it may be attended with so little reaction that it passes unobserved. It is called a hard or Hunterian *chancre*—hard because it is infiltrated with cells, Hunterian after the description by John Hunter.

It is essentially a granuloma, which becomes ulcerated, a point of difference from other ulcers seen on the genitals, but the spirochaete may make its entry through lesions, the main responsibility for which rests with pyogenic organisms, and the acute inflammatory reaction comes on first and obscures the granulomatous. The histology of this stage shows lymphocytes and plasma cells in numbers, often perivascularly, and the arteritis that is common through the whole course of syphilis may be already conspicuous. The lesion takes some time to accumulate enough cells and is therefore not reported by the patient till at least a fortnight after the exposure. He may delay till the nodule has become ulcerated, and ulceration, secondary infection and self-planned treatment may obscure still more the characters of the lesion and make the spirochaete hard or impossible to find. This suggests that all possible lesions in the genitalia, whatever they look like, should be examined suspiciously, and that cleanliness and no antisepsis should be used until certainty has been reached about the presence or absence of the spirochaete.

Fortunately, an extremely characteristic lymph-gland enlargement will be found particularly helpful in the extra-genital or hidden chancre. The draining gland is conspicuously, painlessly and disproportionately enlarged; usually one only, and an indurated rubbery gland; this is much more visible, much less tender and harder than glandular enlargement following a purulent infection. Aspiration from this gland may make the diagnosis when the spirochaete cannot be found in the exudate from the ulcer.

Treated or untreated, the lesion heals up slowly, with a well-marked scar that may be seen years later. Until it heals, the patient is infective; do not handle suspected chancres yourself, but make the patient do any manipulation necessary.

During the later stages of the primary lesion, the antibodies against the inflammation are forming in the body and may be detected in the blood. For the details of the serology of syphilis, and the various tests that may be made on the blood serum to

detect the disease, we refer you to the companion volume on Bacteriology.

(*b*) *The secondary stage of syphilis* is one of generalization throughout the body; lesions are many, spirochaetes many, reaction by the tissues slight or moderate; many patients show no disease during this stage of generalization. Characteristic forms are skin rashes of a coppery colour, variably indurated according to the degree of cellular response to the organisms, and so becoming more nodular in the later lesions; the mucous membrane of the mouth is involved with " snail-track " ulceration of the fauces; the skin in moist situations develops broad flat warty growths (condylomata lata) with cellular infiltration. These are highly infective lesions with many spirochaetes. The secondary stage, like the primary, disappears in a few weeks and passes over gradually into the tertiary stage, which is the stage in which the disease becomes dangerous to the patient.

(*c*) For reasons not yet known, the proportion of persons developing *tertiary syphilis* is about one in four of all those infected, but the majority of these are seriously affected by syphilis of the heart or central nervous system. The characteristic feature of tertiary lesions is that they are relatively few, spirochaetes are very few, but the reaction to them is intense. The lesions can be grouped into: (i) the gumma; (ii) diffuse syphilitic fibrosis—this is the less severe. Neurosyphilis is considered separately (p. 101).

GUMMATA (Plate 6) are lesions in which more or less massive nodules of chronic inflammatory granulation tissue are found undergoing necrosis at the centre; if there is a surface near, this necrotic tissue may ulcerate through. Typical sites for ulcerated gummata are the skin, and the mucosa of the mouth or palate, especially where overlying subcutaneous or submucous bones. Internal non-ulcerated gummata may be found in any organ, but the liver, testis, tongue and heart will account for most. Spirochaetes can only be demonstrated by exceptionally diligent searching, and the characters of the inflammation are not as diagnostic as they are in tuberculosis. The gumma is more fibrous and less necrotic than the tuberculous lesion; the dead tissue in the centre keeps more of its structure and the lesion does not collapse so easily. There are no miliary gummata around, whereas in tubercle satellite lesions are usual. Ulceration in gumma is clean-cut, that in tuberculosis undermined and serpiginous. Histologically, in addition to these points, there is no epithelioid cell zone in gumma comparable to that in tubercle: giant-cells are usually fewer and smaller, the fibrous tissue radiating into the lesion rather than encircling it. The easiest point

of distinction is the site: though rare gummata occur in the lung, the parts favoured are different; coincidence comes nearest in the testis (body in syphilis, epididymis in tubercle), and in bone (ends in tubercle, shaft and subcutaneous bones in syphilis).

The spirochaete has been demonstrated in gummata, but they are present in such small numbers that this is only possible as a research project. The tubercle bacillus is only slightly more easy to find and this is not a very valuable practical distinction. The gumma represents a particularly intense reaction of the body to a small number of spirochaetes—a variety of allergic response, but there is no knowledge of why this change in the attitude of the body to the spirochaete occurs after what may be a long period of quiescence.

DIFFUSE SYPHILITIC FIBROSIS is a similar but less severe reaction which is found (*a*) in the testis, leading to atrophy of the seminiferous tubules, (*b*) in the meninges where it is combined with the attack (*c*) on the arteries which is the most serious of the effects. The inflammation attacks the whole vessel wall, but the important consequence is that the lumen is narrowed by the inflamed intima, and it is therefore often referred to as syphilitic *endarteritis*. It is seen in the meningeal vessels where the loss of arterial blood leads to failure of nerve functions in many widespread parts of the C.N.S.; the segmental distribution of the arteries to the spinal cord brings about one of the more characteristic examples, a transverse segmental defect in the cord referred to as syphilitic transverse myelitis, though it is the vessels and not the cord that are attacked in the first place by the spirochaete. It may, however, affect any small artery, and is often found in the neighbourhood of gummata—it may help in the diagnosis, but endarteritis is so often a complication of simple chronic inflammations that it must never be used on its own to make a diagnosis of syphilis.

A special case of great importance is *syphilitic aortitis*. In this, as in the attack on a smaller vessel, there is an *endarteritis*, so that the intima of the aortic wall is thickened with grey cellular patches bearing irregular stellate scars, and usually almost obliterated by extremely severe secondary atheroma (p. 133); this inflammation spreads to the commissures and the aortic cusps, leading to syphilitic aortic incompetence, and to the orifices and first half-centimetre of the coronary arteries, with deprivation of the blood supply to the heart muscle; these are important causes of disability and death. The thick wall of the aorta, however, is not entirely nourished by the blood in the lumen, but by *vasa vasorum*, and these microscopical vessels in the adventitia and media are also involved in the inflammation; the whole structure of the aortic wall is destroyed,

elastic and muscle both replaced by fibrous scar tissue, which is inadequate to withstand the heart beat and is stretched to form an *aneurysm*. This distended pulsating vessel presses in turn on many important structures in the mediastinum, the trachea, left bronchus, recurrent laryngeal nerve and the vertebrae in particular; fatal haemorrhage may occur from rupture of the aneurysm into pleura or other spaces, though clotting in the sac makes this less frequent. Syphilitic aneurysms may rarely occur on other large arteries, but in small vessels the effect is invariably narrowing by endarteritis and not stretching by destruction of the muscle.

CONGENITAL SYPHILIS (p. 260). This has become a rare disease at the present time, owing to the better treatment of adult syphilis and ante-natal supervision. The affections of the bones (p. 112), nervous system (p. 104), and liver (p. 186) are described briefly elsewhere.

YAWS. This disease, which though due to a *Treponema* (*pertenue*, very like that of syphilis) is not due to veneral contagion, resembles a flamboyant case of secondary syphilis. There is a primary yaw, corresponding to the primary chancre, usually found in children and acquired by contact; it is larger, softer and redder than the chancre because there is more epidermal proliferation and less endarteritis than in that lesion, differences that are conspicuous also in the later stages. The organism is present in numbers. The secondary stage includes widespread skin but few mucosal lesions; they are more likely to occur before the primary has healed, and form a more continuous persistent eruption than the syphilitic eruption. Tertiary lesions include chronic ulcers and gummata which have the same distribution as the syphilitic tertiary lesions, involving the face and palate, the larynx, and subcutaneous bones, but neural and internal lesions are not a common sequel. Peculiar to yaws is a chronic ulcerative hyperkeratosis of the soles of the feet. The histology is like that of syphilis. The two diseases give some immunity against each other, and the serological tests are positive in both diseases. Yaws however yields much more easily and completely to treatment.

Although other spiral organisms infect man, none of them give rise to the prolonged reactions of syphilis and yaws. The more important, due to species of the genus *Leptospira*, give rise to acute febrile illnesses with scattered toxic necroses, notably in the liver, and haemorrhages (Weil's disease); they are derived from reservoir infestations in rats, dogs and other animals. The relapsing fevers are transient spirochaetaemias with splenomegaly but without tissue damage; the organisms are agglutinated and lysed in one febrile attack, the "relapses" being due to survivors (probably antigenically of different strain) building up and being destroyed in

their turn. A large coarse spiral organism is found in oral ulcers associated with a fusiform bacillus (Vincent's angina); it is uncertain whether it is the cause, or merely a saprophytic invader.

Parasitic Infestation

Size and complexity of structure distinguish these from previously described invading agents. The organisms are, however, less numerous individually, more elaborately organized than bacteria and therefore less well able to live outside their host (except in specially designed stages), and more dependent on planned transport to their next host rather than casual contact. The same principles underlie their success; an abundant and usually rapid reproductive rate allowing for wastage, and an illness that is not rapidly fatal, so that there is the best chance of long life in the host and many opportunities to transfer to the next. Close contact with the next host, so that the stage outside is not exposed too long to a hostile climate, is important. Organisms whose method of transport is in faeces are mechanically controlled in civilized countries, but common in those where there is no sanitation—not necessarily tropical, but usually warm and moist for the egg stages to survive; they are rarer where intense heat is associated with desiccation. The second important method of spread is by an insect vector.

Because of these things, parasitic infection is largely confined to poorly organized countries, and of little interest in urban communities; but in such countries it is a major problem. The illnesses caused are mainly mild, chronic or relapsing, or even subclinical, reaching the acute or fatal stages only exceptionally when infection is peculiarly severe or when a new population is involved, e.g. by transfer of troops, transfer of parasites, or sometimes in young children. The damage done by the parasite is only partly direct, much more by paving the way for intercurrent infection with, for example, tuberculosis. But this quiet indirect subclinical disease is far from unimportant; the numerical total of ill-health from parasitic infections is at least as great as that from other forms of disease. The part of the life of the parasite spent between hosts is that in which attack on it is often most successful, though this attack is often a matter of public health and large-scale engineering measures, rather than what is usually considered medical work. It is convenient to consider the parasitic diseases under three heads—

1. Protozoa.
2. Worms.
3. Insects and related forms.

Parasitic Protozoa

Two main groups can be separated: (*a*) those inhabiting the blood and the tissues; (*b*) those inhabiting cavities.

(*a*) Blood and Tissue Forms

MALARIA. A chronic relapsing febrile illness due to the colonization of the red cells by haemosporidia of the genus *Plasmodium*; at intervals of two-three days the infected cells undergo haemolysis with discharge of forms (schizonts) which invade, grow in, and multiply asexually in a further batch of red blood corpuscles. After a period of this kind of reproduction, sexual forms (gametocytes) appear, which can reproduce sexually only when taken into the stomach of a female mosquito which must be of the genus *Anopheles*. The progeny of this sexual cycle find their way into the salivary glands of the mosquito and may, about a fortnight later, reach a new host when it makes a puncture to obtain blood. The injected sporozoites, before colonizing the red cells, undergo a reproductive phase in the liver, which lasts about a fortnight.

Four species of Plasmodium infect humans, with differences of considerable clinical importance; there are other forms in other animals. The details of the appearance of these parasites must be found in larger textbooks.

The effect of this parasitism is primarily a chronic moderately severe haemolytic anaemia of lifetime duration. The infected children are stunted, the adults liable to tuberculosis; they both have spleens which are enlarged because of phagocytosis of the parasitized red cells, and which give an index of the endemicity of the disease. In one form (subtertian or malignant malaria) the intensity of the red-cell infection may be so great that the cells block internal capillaries.

The natural distribution of this disease and the most effective control of it are both based on the presence or absence of the mosquito and of an isotherm of 60° C. necessary for development in the mosquito stomach. The disease therefore at present has only a toe-hold in Britain, but reaches Holland, and is common in the Mediterranean and all warm countries; it is absent in the subarctic though there are many mosquitoes.

Leishmaniasis and *Trypanosomiasis* are other insect-carried protozoan infections found in tropical and subtropical zones. *Toxoplasmosis* is a recently discovered ill-understood infection, apparently widespread judging by serological tests, but producing illness only in babies to whom it is transmitted by the placenta; they

show a chronic meningitis. The reservoir of infection and the manner of transmission to adult patients are unknown; myocarditis and lymphadenopathy are described.

(*b*) Cavity-inhabiting Protozoa

The alimentary tract of wild animals is a home to many individuals and species of parasitic protozoa; in man who cooks or otherwise sterilizes most of his food they are uncommon. Dust-borne cysts will, however, remain alive even after desiccation long enough to bring about disease in the absence of gross faecal contamination of food, and this is the source of *amoebiasis*, infection of the gut by the pathogenic *Entamoeba histolytica*. Although referred to as amoebic dysentery, the term is misleading in that, except in advanced cases, the alimentary tract symptoms are slight and there is no primary inflammation of the gut at all. The specific name *histolytica* gives the key to the action of the amoeba; it is capable of dissolving cells with which it comes in contact, without exciting any inflammatory response. The primary lesion is the digestion of a few mucous cells in the caecum or colon allowing the amoeba to enter the submucosa and digest rather more widely there; a flask-shaped ulcer results with a narrow opening (often diamond-shaped as seen by sigmoidoscope) and no reddening of the surrounding mucosa. The digested areas widen, become rounded and confluent with the extension of the disease. A serious complication is the invasion of a portal venule by the amoeba so that it reaches the liver in the blood-stream, and may spread to the lung; in these situations, exactly as in the gut, it digests the surroundings without pus formation (none the less called amoebic abscesses).

Other gut protozoa are described, some apparently pathogenic, others saprophytes. A multi-flagellated protozoon, *Trichomonas vaginalis*, is not uncommon in vaginal discharges; it is transmitted by sexual intercourse and appears to be responsible for the vaginitis and not merely a saprophytic casual invader.

Worms

These are often (but by no means always) conspicuous creatures whose presence was known in early human history. The zoological descriptions have been more than usually roughly handled by the systematists, with the result that one worm may be known by several names. This confusion is one source of difficulty; another is the involved nature of the detailed anatomy and stages in life-cycles. Much of this can be left to zoological textbooks. Three classes provide parasites—

1. The flatworms, flukes or *trematodes.*
2. The tapeworms or *cestodes.*
3. The roundworms or *nematodes.*

1. TREMATODES. Some free-living forms in nature, many parasites in all classes of animals. Mainly hermaphrodite, flattened leaf-like organisms, up to half an inch long, with no gut or only a blind gut. The human group all require at least one intermediate stage between two human hosts, in which a mollusc is vector; this stage of development is essential for the parasite, but the detailed morphology and nomenclature thereof is not essential for the doctor.

The most important example, by way of a type description, is the genus *Schistosoma* (*Bilharzia*) in which the adults inhabit veins in the abdomen—the vesical in the species *Schistosoma haematobium*, the portal and colonic in *S. mansoni* and *S. Japonicum.* This particular genus is not hermaphrodite, but the males carry the females in a split in their body, from which the generic name is derived; the older name still in use commemorates a German morbid anatomist who elucidated the disease. The gravid females migrate to the mucosa of the bladder or colon respectively and there lay numerous spined eggs, which ulcerate or are thrust through the mucosa and so excreted into water to reach their intermediate host, a fresh-water snail. The larvae return to the water; they then bore through intact skin to reach the circulation and are transported to their destination. Cystitis or dysentery results from the egg-laying activities. Although curative drugs are known, the most effective attack is on the snail which is an essential part of the transmission of the disease.

The lung fluke (*Paragonimus*) and the liver flukes (*Fasciola* and *Clonorchis*) of the Far East inhabit the bronchi and the bile-ducts respectively, and have intermediate stages in crabs and snails.

The inflammatory reaction of the body to the presence of all these worms is a non-specific chronic lymphocytic and plasma cell reaction with much fibrosis.

2. TAPEWORMS (CESTODES). The adult (definitive) stage of these creatures, which always inhabits the gut, is a tape-like structure from a few millimetres to many metres long, with at one end an organ of attachment called a *scolex*, which has suckers and hooks of importance in identification of species. This is colloquially called the head, but has no organs of vision, mouth, or other structures normal in a head. Behind come a series of segments (*proglottids*) increasing in maturity and size, provided with one or two sets of gonads which fertilize those of other segments or their own, and

at the other end of the worm being merely egg-bags. Nutrition is by diffusion, as there is no gut; some species show a highly selective uptake, e.g. vitamin B_{12} by *Dibothriocephalus latus*, a tapeworm derived from fish; the wasting clinically observed in the host of the common tapeworms may originate similarly. Otherwise the adult stage causes little illness. Two large forms, *Taenia saginata* which has its cyst stage in the ox, and *Taenia solium* which has it in the pig, occur in man; there are a number of smaller species of less importance.

Transmission of the eggs in the mature segments to another animal is essential in the development of cestodes; in this second or intermediate host the larvae form cysts in internal organs, these differing in their structure very widely. The normal life-cycle, therefore, is: a carnivore containing the adult tapeworm polluting herbage eaten by a vegetarian animal which develops the cyst; eating the cyst in its prey the carnivore acquires the tape form. In two species, an abnormal cycle results in cyst formation in man; one, the *hydatid cyst* derived from a minute dog tapeworm (*Echinococcus granulosus*) whose proper intermediate host is the sheep, the other an aberrant cyst stage of the tapeworm *T. solium* which normally occurs in the pig; but if food is ingested contaminated with human faeces containing the proglottids of the tapeworm, these can develop in the human. The main incidence of these two diseases is therefore hydatid in sheep-raising countries, the *T. solium* cysts in places where human manure is used.

These cyst stages are serious. In the hydatid, a larva hatching in the gut bores straight through into adjacent structures, especially the liver, and then forms a *primary hydatid cyst*; this has a lining which buds off a number of daughter cysts, and these do the same; in the smaller cysts the epithelium forms a number of scolices which project into the lumen of the cyst and contain the hooklets that attach the mature creature to the intestinal wall. These are characteristic microscopical objects. The outer wall of the main cyst is a friable and slippery membrane of chitin; outside this the host builds up a fibrous chronic inflammatory capsule. Until this is complete there is a possibility of rupture of the primary cyst, liberating viable daughter cysts into the blood-stream to form *secondary hydatids* in distant organs. The cysts grow to about two inches and cause symptoms by pressure as benign neoplasms do. Absorption from the cysts causes an eosinophilia in the blood, and the development of antibodies which can be made use of in diagnosis, either by complement fixation or by an intradermal test (Casoni's test).

The cysts of *T. solium* are zoologically called cysticerci, and the

disease when they are found in the human is therefore known as *cysticercosis* (in the muscles and fat of the pig as cysticercosis cellulosae, or measly pork). The subcutaneous and intra-muscular cysts in man are insignificant, oval cysts about half an inch long which die and calcify; they may be palpable. or diagnosed by radiography. Unfortunately the cysts may be present in some numbers in the brain, causing epileptic fits and mental damage.

3. ROUNDWORMS OR NEMATODES. This group of highly successful organisms has colonized almost every possible parasitic or free-living habitat, with a highly simplified anatomical structure making them very alike, as if machine-made articles. The sexes are separate; the worms have a tough cuticle, few sense organs, large gonads, and an alimentary tract. They are white tapering smooth worms from microscopic size upwards. The numerous parasitic forms differ clinically widely in their effects. They can be classified practically as follows, though not zoologically: (*a*) those inhabiting the blood and tissues; (*b*) those inhabiting the gut as adults, but with a larval blood and tissue stage (this is the most important group); (*c*) those wholly confined to the gut.

(*a*) *The Blood and Tissue Nematodes.* Examples are *Filariasis*: adults in the lumbar and inguinal lymphatic glands, causing symptoms by chronic lymphatic obstruction; larvae in the blood, carried to the next host by a blood-sucking mosquito. *Onchocerciasis*: adults in a fibrous mass in the subcutis; larvae around these swellings are carried to the next host by blood-sucking flies. *Dracunculus* (guinea-worm): adult females in the subcutis, discharging their eggs to the exterior by an ulcer; there are larval stages in water and in a water-flea, swallowed with water and growing to maturity in the retro-peritoneal tissues from which the females migrate after fertilization. This group is almost entirely tropical or subtropical because of the distribution of the insect vectors and the need for warmth while outside the human body.

(*b*) *Those with a larval stage in the tissues, but living as adults in the gut.* The most widespread and important are the two species of *hookworm* which inhabit the small intestine in numbers sufficient to counterbalance their size ($\frac{1}{2}$ in.) and cause symptoms by bringing about a severe chronic anaemia. This may be due to actual blood loss through the alimentary tract of the worms, which grip the mucosa with their mouth capsule, or to deviation of essential food. The eggs are laid in thin-shelled capsules and develop rapidly in the faeces, remaining viable for some time in moist surroundings. The larvae penetrate skin directly, with local irritation, and make their way to the gut by the blood-stream, and lungs, as *Ascaris* does.

Plate 7. Rheumatic Disease

(*a*) Fibrinoid necrosis of collagen in the subcutaneous nodules of rheumatoid arthritis. In the upper half strands of collagen are crossing in a dark structureless material which has some of the reactions of fibrin. Polymorphonuclear leucocytes are just visible among this, but no living cells. A palisade of darkly staining macrophages lies below this and fibrous tissue outside that again. × 80.

(*b*) Aschoff nodule in the myocardium. The fibrinoid necrosis is represented by the wispy material in the centre. Between this and the cardiac muscle fibres is a collection of cells, the most characteristic below—large basophil often multinucleate cells; the rest include lymphocytes and fibrous tissue. × 200.

(*c*) Active rheumatic valvulitis. The surface of the valve cusp below is covered with a thick layer of fibrin and platelets. Growing out of the substance of the valve into this, and so fixing it firmly to the valve, are many of the basophil histiocytes like those in (*a*) and (*b*) above. No polymorphonuclear leucocytes or bacterial colonies are seen. The valve itself has become very cellular and there are small blood-vessels in it. × 80.

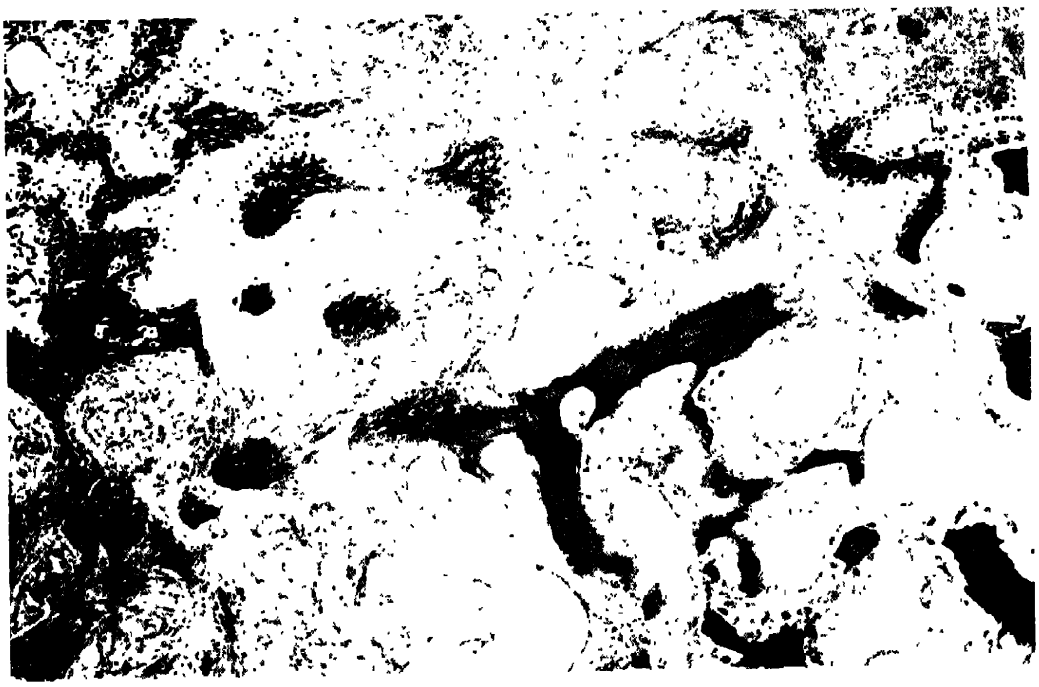
(*d*) Later quiescent valvulitis. The fibrin and the greater part of the histiocytes have now disappeared, but there is an increase in the fibrous tissue in the cusp, often parallel-fibred or laminated. As this matures, the collagen becomes more dense and the cells disappear, rather as in Plate 2; calcification in the dense fibrous tissue is common. × 80.

(*a*)

(*b*)

(*c*)

(*d*)



(*a*)

(*b*)

(*c*)

Plate 8. Bone Pathology

(*a*) Early callus. Fracture below and to the right. Extremely wide vascular spaces in the aseptic granulation tissue; large multinucleate osteoclasts are removing the three pieces of bone in the bottom right. In the more fibrous zone a little further in, new bone formation is going on around the biggest fragment; in some of this the line of osteoblasts shows that this is lamellar, but elsewhere woven bone is being built out into the fibrous tissue. Further out still in the upper left and across the top, woven bone is being formed in the fibrous tissue without any pre-existing scaffolding. The cellularity and fibrous texture of this bone should be contrasted with the normal; woven bone is always pathological after the first year of life. × 40.

(*b*) Late callus. A vertical fracture through the articular cartilage and the underlying bone (right top) is now firmly united by the oblique bar of new bone; this is of complex origin. New lamellar bone (slightly darker than the original bone at the right) has been laid down over this bone, over the cartilage, both the large and the small fragment, which is thereby incorporated in the callus, and over much of the rest of the bone; but the centre of the oblique fragment and the middle top piece have the cellularity of woven bone; woven bone is a temporary measure only. The callus though still vascular is less so than above; there is more fibrous tissue. × 40.

(*c*) Paget's osteitis deformans. This higher magnification (× 85) shows better the multinucleate osteoclasts, and the layer of osteoblasts with the poorly calcified osteoid zone below them; the cement lines are also conspicuous, marking the junction of bone formed in the numerous separate minor episodes of local bone formation and destruction which make up the disease. The details of formation and destruction are normal in themselves; it is the vigour with which they are carried out and the lack of ordered plan in the bone physiology that is abnormal.

The common roundworm *Ascaris lumbricoides*, although living in the gut and transmitting its eggs to the next host via the faeces, falls into this group because of the extraordinary migration undertaken by the larvae, which hatch in the small intestine and then burrow through into the blood-stream, and so to the liver and the lungs; they then reach the bronchi and pharynx, are re-swallowed and finally settle down when they next come into the small gut. During their passage through the lungs they may give rise to a mild inflammation; otherwise their presence is not as a rule serious, though they migrate about the alimentary tract and its openings and so come to medical notice.

The third important member of this set is *Trichina* (*Trichinella*) *spiralis*, an unusually widely distributed parasite that causes the disease trichiniasis. Most parasites are strictly limited to one or to a very few species; but man, pigs, rats, cats and a large number of other hosts of trichina are known; they must all be partly carnivorous. The adult worms, 1-3 mm long, live for about six weeks in the gut, producing larvae which migrate into the blood-stream and thence to voluntary muscles where they develop; those reaching heart muscle may develop partly, those ending in other tissues die. In the muscle they encyst, the larva coiled up in the spiral which gives it its name, and wait to be eaten by the next host. Symptoms are caused during the migration if the larvae are numerous, but it is on the whole a well-tolerated parasite.

Although chemical poisons are known which are lethal to the worms preventive measures based on the life-cycles are the successful way of diminishing diseases of this kind.

(*c*) *The Gut-inhabiting Nematodes.* The adults live in the gut, usually the large gut, pass their eggs to the exterior, and transmission is by swallowing without any intermediate host or migration. The common trivial but annoying worm *Enterobius* (*Oxyuris*) *vermicularis*, the pin-worm or thread worm, is the only individual species of importance; the mature female migrates to the anus to lay her eggs and causes irritation as she does so; scratching transfers the eggs to the fingers and re-infection is direct.

Insects and Mites

The principal importance of blood-sucking creatures in human disease is in the transmission of infectious organisms by the bite: examples of this are found in every class of pathogen: viruses (yellow fever), rickettsiae (typhus), spirochaetes (relapsing fever), bacteria (plague), protozoa (malaria) and worms (filariasis). Their effects are exceedingly important and the distribution of many of

these diseases is determined by the distribution of the insect vector. The details of their zoological classification and life-histories will be found in larger books. The majority of these visit the human for brief periods only to feed; a small number take up their residence on the body or clothes. These include the two common forms of louse and the scabies mite.

The body louse (*Pediculus corporis*) inhabits the clothes of uncleanly persons, feeding on the blood; a variety, the head louse, lives and lays its eggs (nits) on the hair. Irritation causes scratching and septic skin lesions, and the lice may carry typhus. The crab louse (*Phthirus pubis*) lives attached to the hair of the pubis and occasionally other body hair and eyelashes, but not head hair; local irritation is marked, but this form carries no disease.

The scabies mite lives on the skin, the gravid females burrowing in the epidermis. The importance is irritation and scratching, and secondary septic infection; no disease is carried.

The parasites spread from one host to another by close contact, the lice but not the scabies mite being transmitted also by clothing.

ALLERGIC INFLAMMATORY REACTIONS

This is the most difficult group of inflammations to understand, the basic point being that this reaction is an individual peculiarity of the patient. In the most familiar examples (sufferers from asthma or hay fever) contact with substances which bring about no noticeable response in the ordinary man results in severe symptoms of breathlessness or rhinorrhoea. The reasons for this sensitivity are not fully known; the majority of sufferers have relatives similarly afflicted and the possibility of genetic abnormality is high.

Somewhat similar sensitivity may be developed in previously normal people or experimental animals as the result of bacterial infection. In both groups there is stimulation of the antigen–antibody reaction in an abnormal manner; in the first group antibody is often demonstrable in the serum, in the second it appears all to be fixed to cells. For ease in discussion the reactions can be divided into three groups—

1. Immediate reactions, resembling the pharmacological actions of histamine in the effects, often unrelated to infection at all, frequently with demonstrable circulating antibody, amenable to treatment with anti-histamine drugs (sometimes called "anaphylactoid").

2. Delayed cellular reactions, of an inflammatory type, usually related to bacterial antigens, without demonstrable circulating

antibody, without resemblance to the action of histamine and not amenable to anti-histamine drugs, but reacting to cortisone.

3. Auto-immunization, resulting from the development of antibody to antigens in the body's own tissues.

The term " allergy " is loosely used to cover all these reactions as well as some others, and implies unusual sensitivity in the patient to some particular antigens, very often a single one. It was originally coined by von Pirquet in 1906. He pointed out the alteration in response (the literal translation of " allergy ") which occurs when an animal that has received one injection of tubercle bacilli receives a second one; the response might be increased (" hyperergy ") or diminished (" anergy "). These two terms have dropped out, and the original transferred to mean an increased reaction to a previously received antigen. In the second group the antigen is usually bacterial, though it may not be; in the first group, it is usually not bacterial though it may be. In both cases it is an abnormal personal variation on the antigen antibody reaction; the reasons for the difference are not clear; in one group the antibody is apparently still circulating in small quantity, in the other it is all fixed to the cells.

The main importance of the concept is that it turns attention away from the bacteria and back to the patient in whom these organisms are producing disease, a salutary reorientation after decades of intensive bacteriology at the start of the century. Two very good examples of this are *rheumatic carditis* and *acute nephritis* in both of which streptococci in the throat, which normally set up a straightforward purulent reaction, produce in certain individuals a very different kind of reaction at a distance from the organisms. Why these people should be so affected in contrast to the ordinary man is uncertain; attempts to link up with other observable and possibly hereditary characters were made by the physicians of the past century in what they described as the rheumatic " diathesis " or tendency. Since this is an individual reaction, and since some forms of sensitivity are hereditary, there is nothing improbable in a familial tendency to rheumatism or a linkage with red hair or certain types of teeth, such as our grandparents observed with great detail if perhaps a little uncritically; our more modern science has nothing yet to put in their place in picking out those who are likely to show this response, and observations of this sort need not be despised because there is no apparent scientific rationale for them.

1. HISTAMINE-LIKE SENSITIVITY REACTIONS. The exciting agent (allergen) is of various sources, but foodstuffs, animal and vegetable dusts make up the majority. It is usually a protein (though a few

bacterial polysaccharides also are antigenic); where a drug, not itself a protein, is apparently the cause, there is reason to believe that it becomes linked to a protein before it can act as an allergen, though the antibody that results may react later with the drug alone. The antibodies are present in the serum of the sufferers and may be demonstrated by reactions *in vitro* or by transference in injected serum to another human, not previously sensitive.

The reactions in the patients take the form of (*a*) spasmodic constriction of the bronchial muscle (asthma) associated with the secretion of mucus; (*b*) vomiting and diarrhoea (food sensitivity); (*c*) over-secretion of nasal mucus with oedema of the mucosa (hay fever); (*d*) erythematous and vesicular eruptions on the skin (urticaria, erythema multiforme, toxic erythema). The reactions may be almost immediate following contact with the offending substance, which is thought to react with antibody fixed to the cells of the part concerned. This fixation of antibody and histamine-like action in contact with the antigen can be shown *in vitro* with the uterine muscle of the guinea-pig. The reactions can mainly be closely paralleled by the pharmacological action of histamine and are not specific to the antigen; very varied antigens can have the same final common action in this way. Of great practical importance is the value of anti-histamine drugs in the treatment of this kind of sensitivity.

Histological examination of this reaction is not commonly made with the exception of the polypoid nasal mucosa (" nasal polyp " of the aural surgeon); this shows an oedematous submucosa with a well-spread out infiltration of inflammatory cells of all sorts, plasma cells and eosinophil leucocytes predominating. Eosinophils may be present in the bronchial secretion as well as in the bronchial wall in asthma.

An example of this sensitivity that was formerly common is serum sickness; when a considerable volume of horse serum was injected into a patient to provide passive immunity, it acted also as an antigen, and about ten days later antibodies to it would be present; the large quantity of antigen might not be completely disposed of, and reactions between it and the new antibody would occur in the shape of joint pains, urticarial rashes, fever, and sometimes gastro-intestinal symptoms.

2. CELLULAR INTENSELY INFLAMMATORY SENSITIVITY REACTIONS. The first one to be described was that of Arthus, who showed that if a rabbit was repeatedly injected with the same antigen (horse serum) the reaction became progressively more intense until actual necrosis at the site of injection occurred. No circulating antibody can be shown, as it is all fixed to the cells at the site of reaction;

this fixation can occur either with the antigen or the antibody, the reaction occurring when the corresponding antibody or antigen is injected. This is a rapid reaction; but the more slowly developing "delayed" reactions in tuberculosis, those of von Pirquet and Mantoux, similarly consist of an increasing inflammatory and necrotizing reaction to the injection of small quantities of tuberculin. These reactions are not simply that following liberation of histamine, and they are not controlled by anti-histamine drugs. Histologically, there is an acute inflammatory response, though without demonstrable organisms; in some cases (erythema nodosum occurring in tuberculosis and similar "tuberculides") there may be features recalling the ordinary inflammatory response to the organism.

Clinically, this sort of sensitivity is thought to underly the changes in response to the organism that develop in the long course of tuberculosis, acquired syphilis, and some others, and to be at the back of the "collagen diseases" discussed later (p. 97). There is no hereditary tendency proved in this group of sensitivities, and there is no particularly frequent association between the two types of sensitivity in patients.

3. AUTO-IMMUNIZATION. This concept has been developed fairly recently to account for some diseases which have an apparently chronic–inflammatory histology, but in which no infective agent has ever been shown in spite of strenuous efforts. Often there are features in the patient suggesting an inflammation, sudden febrile illness, or local redness heat or swelling.

The best example is the uncommon disease known as lymphadenoid goitre, or Hashimoto's disease of the thyroid gland. In this, the gland becomes hard, white, and swollen, the gland acini disappear and the tissue is infiltrated with lymphocytes and, more significant, plasma cells. In the early stages thyroid function is depressed, in the late the whole gland may become fibrous. This histological course is suggestive of a very low grade inflammatory process, and the plasma cells show that antibody is being formed. Roitt and others in 1956 demonstrated that the antigen was almost certainly thyroglobulin, the form in which thyroid hormone is stored in the gland but which does not normally leave the thyroid acinus; so the body regards it, when it does, as a foreign substance. Here then is an example of the body forming antibodies against its own tissues.

The suggestion that the same sort of mechanism lies behind other disease has naturally been made. It is especially applicable when an apparently inflammatory process shows no clinical evidence of contagion, and when neither histopathological nor bacterial nor

virus studies have been able to show after an exhaustive search any causative organism. Although the inability to demonstrate bacteria or viruses in lesions does not entirely exclude their presence, since cultural specificity for some may be very high, when this is coupled with no trace of clinical contagion it is presumptive evidence that something outside the ordinary causes of inflammation should be looked for. If the histology shows the presence of antibody-forming plasma cells, the evidence is stronger and much of what has previously been classed as non-specific chronic inflammation on histological grounds is due to be re-examined in the light of this possibility.

When an eye is so injured that the uveal tract is involved, ophthalmic surgeons have noted inflammation arising in the opposite uninjured eye some ten days later, often going on to destroy vision. This " sympathetic ophthalmia " is not due to bacterial infection, which may be slight or even absent in the injured eye and is always absent in the second eye; indeed if the first eye is destroyed by gross purulent inflammation sympathetic ophthalmia does not occur. It is probable that antigen liberated into the blood from the injured uveal tract produces antibodies which react with the uveal tract of the sound eye as well as with the damaged eye.

Two other diseases where these concepts of allergic inflammatory reaction have proved most useful must now be studied. In both, there is apparently an inflammatory reaction in which bacteria and viruses have never been satisfactorily demonstrated, in spite of much work and some reports of success.

Rheumatic Carditis

This is a recurrent disease, affecting the heart seriously, and joints and subcutaneous tissues less seriously, in which nodules of chronic inflammatory granulation tissue of a specific histological pattern are constant. There is no case-to-case infectivity, and no bacteria behaving normally have been shown in the lesions. A few authors have described streptococci in the lesions in very small numbers, but if this is true and not due to contamination, the bacteria are behaving in a manner totally different from the infection set up by streptococci elsewhere and in ordinary people.

The connexion with streptococcal infection in the throat was made first on clinical observation. When children suffering from rheumatic carditis were collected for long-term treatment and education in special hospitals, it was seen that if there was an epidemic of streptococcal sore throats, about a fortnight later there were a number of relapses of rheumatic carditis. When the infection was due to other organisms, this did not occur. The streptococcus had

to be of a certain group (Lancefield group A, see Bacteriology) and this organism was harboured by rheumatic children far more frequently than by controls; and moreover the antibodies formed to it by rheumatic children appeared more slowly, rose to a higher titre, and persisted longer than in controls. If the sore throats were suppressed by treatment with sulphonamides, the relapses did not occur, but sulphonamides had no effect on an established relapse. The clinical proof was pretty complete that this infection was due to throat streptococci, but they were not acting in these patients as in normal people; the time relation was that of an allergic response, though where in the process of the infection the allergen lay is not yet clear.

Morbid anatomy gave no help beyond excluding ordinary types of infection, and for a long time experimental confirmation of the theory was not forthcoming; but in 1950 it was shown that streptococci intradermally injected into rabbits produced a bacterium-free lesion in the heart that had the histological features of the rheumatic nodule in the human. A persistent focus of a particular strain of streptococcus appears to be essential, as well as a particular human being; for many people are infected with the same strain and develop only a sore throat, or nothing at all.

The lesion in rheumatic carditis is based on a highly characteristic minute focus known as the *Aschoff nodule*, after the great German pathologist who first described it fully. Individually below certain identification by naked eye, they are commonly aggregated and appear as grey beady translucent nodules about match-head size. They are found in the valvular endocardium, at the point where the cusps meet in closure (" contact margin ") spreading up the adjacent mural endocardium particularly on the posterior left atrial wall; along the small branches of the coronary arteries in the muscle; and in severe cases on the pericardium, where there is a fibrinous inflammation with many polymorphs, but no pus and no organisms to culture. The stages of the histology are shown in the photographs (Plate 7). In the middle of those found in solid tissues, and on the endocardium of the valves, there is a streak of material which is referred to as " fibrinoid necrosis of collagen " because it stains histologically like fibrin and contains no living cells; fragmented nuclei are seen around it. Where this material, as on the valves, is in contact with the blood, fibrin and platelets are present in it. Around this is the essential part of the lesion, a group of large polygonal cells with basophil cytoplasm and often two or three nuclei; these are in the main modified histiocytes, but the resemblance of the nuclei to those of muscle have led to the term " myo-

cytes," which could be true in the cardiac lesions but could not be applied to the similar cells that are seen where there is no muscle from which to derive them. Other inflammatory cells are often present in small numbers. The lesion takes months to evolve, and slowly becomes fibrous; the characteristic macrophages either move away or change their form to fibrocytes, and the nodule becomes a concentric laminated mass of fibrous tissue. The repeated formation of these nodules and contraction of the scar tissue leads to deformity of the valve cusps, which are neither pliable enough to close exactly nor flexible enough to open fully to allow the passage of blood. Stenosis (narrowing) or incompetence of the valve results; the mitral valve suffers in every attack, the aortic often, the tricuspid sometimes, but the pulmonary valve is nearly exempt; this is the order of the pressures against which they have to close.

There are other curious features about the disease. The tendency to recurrence is not at all surprising if it is due to a peculiar personal reaction to a fairly common micro-organism, nor is the frequency with which physical traits have been thought to be linked to the tendency. There is an unexplained great increase in the requirements of vitamin C; there is a pronounced relation to sex: the female is the more frequently attacked, but the male cases may be the more serious with aortic as well as mitral lesions. The disease changes its character after puberty; till then, there has been much damage to the heart, and little or no arthritis; after puberty the arthritic side becomes more and the cardiac side less prominent. The arthritis, like the attack on the central nervous system (St. Vitus' dance, Sydenham's chorea), are troublesome while they last but leave no after-effects; the skin nodules which mark a severe attack are of diagnostic importance only.

BACTERIAL ENDOCARDITIS. The contrast between rheumatic carditis and that due to actual bacterial infection of the valves is instructive. In the allergic infection, the lesion is a chronic granulomatous nodule, firmly incorporated in the substance of the valve, healing by fibrosis without much destruction of valve substance. When even relatively harmless bacteria, like the *Streptococcus viridans* which is a harmless commensal in the mouth, effect a lodgement on valves, the inflammation is a sharp fibrino-purulent one, with massive fibrinous vegetations built up on the surface of the valve, full of colonies of micro-organisms and polymorphonuclear leucocytes. The digestive action of the enzymes of the latter break up the valve (hence the alternative name, ulcerative endocarditis); the blood-stream carries away fragments of the fibrin and bacteria to end up as infected emboli in distant organs (p. 143).

Two distinct varieties of the disease are known—the commoner, *subacute* bacterial endocarditis, due to the *Streptococcus viridans*, which can make a lodgement only on a valve weakened by congenital malformation or preceding or active rheumatic infection; starting from some trivial injury to the buccal mucosa such as dental extraction, and giving rise to emboli which are only feebly infected. On the other hand we have the *acute* bacterial disease, with vigorous organisms attacking healthy valves, often derived from a visible source elsewhere in the body, and causing septic infarcts when they form emboli; almost every known bacterium has caused this kind of endocarditis on occasion. In both diseases the diagnosis may be obscure, presenting as a fever with no definite features; sooner or later to the evidence of a septicaemia (fever, splenomegaly) will be added embolic accidents and signs of often rapidly changing cardiac valvular damage. The minor embolic accidents of diagnostic value have been given picturesque names—Osler's nodes after the physician who first described the disease clearly, splinter haemorrhages under the finger nails, the flea-bitten kidney with the glomerular emboli which may show up in life as microscopic haematuria.

Nephritis

One form of nephritis, in which an inflammatory response without demonstrable micro-organisms is found, has again a close relation to streptococcal inflammation in the throat; this may be *accompanied* by an attack of haematuria due to " toxic " action on the kidney, which is transient and of which the morbid anatomy is unknown at present—this is known as *acute focal nephritis*. A much more serious inflammation *follows* the sore throat at the interval of about one week to fourteen days, which we associate with the period of formation of antibodies. In this, *acute glomerular nephritis*, haematuria and oliguria occur, accompanied by a spasm in the small arterioles that results in an increase of the blood pressure, and a toxic effect either on the capillary wall or on the renal tubular function which leads to a general oedema of slight to moderate degree. These effects are reversible, if the patient is well treated, and most do in fact recover; in the few which die in the acute stages, a great proliferation of the epithelium of the glomerular tuft is found, with polymorph leucocytes both therein and in the tubular lumen, where with desquamated cells and protein they form *casts*. In this inflammatory exudate organisms have never yet been demonstrated, though the association with streptococcal infection is regular if good histories are available; usually in the throat, but sometimes elsewhere. The association with *scarlet fever* was long known clinically; this fever

was a streptococcal infection of the throat accompanied by a toxin secretion into the blood with a violent action on the skin capillaries; it has become very rare in the last ten years. The later sequelae of this disease in the kidney are deferred till ischaemic and toxic changes have been studied (p. 191).

The evidence that this is an allergic response to a streptococcal throat infection is supported to a slight extent by experimental work in which antigen–antibody reactions taking place in relation to the glomerular membrane have been followed by similar pictures, but the proof is not yet complete. Certain particular strains (" types ") of streptococcus have been incriminated, but even with these strains the incidence of nephritis is sporadic, and an individual peculiarity must be postulated.

Allergic Angiitis

In both these preceding diseases the vascular system is involved, the heart in rheumatic fever, the arterioles and capillaries in nephritis. Considerably rarer, but included in the list of allergic vascular responses, must come the condition known as polyarteritis nodosa, of which there are several variants. This disease has followed sensitization to drugs, particularly the sulphonamides, and shows itself as a widespread fibrinoid degeneration of the arteriolar wall in many small foci throughout the body; the symptomatology is therefore very varied, but hypertension, renal involvement, and vague effects of arteriolar lesions in the muscles and peripheral nerves are common. Eosinophilia in the peripheral blood may be found, as a mark of allergic response, but it is not noteworthy in nephritis or rheumatic fever in spite of the belief that they are allergic. Pulmonary involvement to a striking extent has been seen. The disease seems to be becoming commoner, possibly because more drugs are now in use to which allergic responses may be formed. The hypertension and renal failure may lead to death.

The Collagenoses

Under this rather unsatisfactory title a number of uncommon diseases are grouped in which *fibrinoid necrosis* of the collagen is seen histologically. Some may have an allergic background; in others the effects on the collagen seem to be secondary. These diseases include rheumatic fever and rheumatoid arthritis (p. 113), possibly nephritis, polyarteritis nodosa, disseminated lupus erythematosus, scleroderma and dermatomyositis; they are so varied and many so rare that only the major ones can be described in this

book, and the term is at present a convenience for cataloguing rather than a contribution to understanding the diseases.

Although some are demonstrably related to sensitivity to drugs (perhaps again particularly sulphonamides) they are not particularly seen in people who are prone to hay fever, or asthma or the other common sensitivities; in this they resemble the type of delayed bacterial response to tuberculin; the two groups of conditions commonly included in " allergic " disease are not clinically associated.

Autoimmunization as a cause of destruction of red cells and platelets has been described.

Inflammation in the Nervous System

Differences in the response to injury in the nervous system make it desirable to consider further details even in a brief survey. The basic principles of inflammation are not greatly modified.

The *mesodermal* cells behave as they do elsewhere. The neural cells proper include first the *neurones*. These are nearly unique in the body in being unable to re-develop following any destruction; once the cell is dead there is no replacement. The cell body contains one conspicuous cytological feature, the Nissl substance, a cytoplasmic nucleotide disposed in angular lumps throughout the cell body except at that part from which the axon arises; this material is destroyed or dissolved in the cell in injuries which do not cause necrosis, and its absence in a section therefore indicates sublethal damage; disappearance of the nucleus marks the later stage (necrosis), after which the cell disintegrates and is removed by phagocytosis. In addition to cytological changes, the myelin sheath which surrounds the axis cylinder provides a very useful method of studying damage to the parent neurone. If the neurone or its axon is destroyed, the myelin sheath breaks up and is removed by phagocytosis; the breaking-down myelin during this process and the absence of myelin when it is complete are both easily shown by histological methods; since the axons of many cells may be collected for easy observation in a tract, study of the degeneration of the myelin is often more convenient and definite than the cytology of the neurone. The breaking-down myelin of the first weeks after the injury can be seen with the naked eye, cream against the normal white, when a large enough area is affected, and simple fat stains are useful; it is stained black by the *Marchi* method with osmic acid. The absent myelin, when the dead myelin is cleared away after six weeks, can be demonstrated by staining the healthy surviving myelin black, in the *Weigert-Pal* techniques with mordanted haematoxylin; the white patches are the abnormal ones. Since myelin

once lost is not regenerated within the C.N.S. (though it is regenerated in peripheral nerves) this method will demonstrate the loss of the neurones for the rest of the patient's life, but it will not give direct evidence of the reason for this loss (Plate 10).

The *neuroglia* form a second important group of cells in the nervous system. They include the *oligodendroglia*, numerous cells related to the maintenance of the myelin sheaths, but not directly concerned in inflammatory processes to any extent. The *astrocytes* can with a little licence be compared to the fibrous tissue of the body; they form dense glial-fibrous scars (gliosis) of different material from collagen and taking much longer to form, but with functions similar to fibrous tissue in other inflammation. When much neural tissue is lost these glial scars may be seen as greyish plaques and streaks, responsible for the hardness that gives the name to the plaques of disseminated sclerosis.

The (mesodermal) *microglia* are phagocytes almost equivalent to the macrophages of the rest of the body, but differ in not taking up material from the blood-stream except where there is injury to the brain. Otherwise they are exactly comparable; because of the amount of lipoid in the brain and the fluidity of the tissue when damaged, they are commonly seen in a foam-cell role and referred to as compound granular corpuscles (Plate 9).

The *cerebro-spinal fluid* is a factor of great import in inflammation in the skull. It undergoes a circulation which can act as a vehicle for the distribution of infections; it occupies a space that is filled by the exudates of some inflammations; and its circulation requires the patency of three narrow places: the aqueduct of Sylvius, the foramina of the fourth ventricle, and the opening through the tentorium largely occupied by the brain stem. If any of these are blocked, the formation of the fluid in the ventricles of the hemispheres is not upset, but the sites of absorption over the cerebral convexities cannot be reached; a state of internal hydrocephalus develops, compressing the brain against the skull, and perpetuating itself by thrusting the temporal lobes down into the tentorial notch. These complications may come on only when the inflammation is over—post-inflammatory fibrosis in the posterior fossa following mild otitic or other infections of the meninges. They may also occur from purulent exudate in the acute stages; a further mechanism by which the brain is compressed, in addition to the more obvious one that inside a closed box like the adult skull there is no room for the exudative events of inflammation; the unossified sutures of the child and still more the fontanelles of the infant may allow a little relief.

Purulent Inflammation

The sources must be either *direct injury* from compound fractures of the skull; spread from adjacent infected *foci*, of which the middle ear and the nasal sinuses are the most important; a special case combining these two occurs where there is injury to the ethmoid-orbital plate of the frontal bones, from fracture of the skull or penetrating wounds of the nose, orbit or forehead; these put the bacteria of the nasal cavities in communication with the meninges, and surgical closure of such communications is desirable to forestall this infection; such communication may declare itself by a leak of cerebro-spinal fluid from the nares, but this may not be conspicuous. The third possible route of infection is by the *blood-stream.*

Foremost among the sites that give rise to pyaemic infection of the brain comes pulmonary suppuration in any form, lung abscess, chronic empyema, and bronchiectasis, and as long as such foci are present the patient is always at risk from cerebral metastasis. Infective endocarditis may lead to infected infarction (p. 143), and there are other primary sites. The abscesses are usually multiple, acute, and fatal through cerebral compression by the inflammatory oedema around them. Where the infection spreads from adjacent foci, the abscess is usually single, and forms less explosively; and though there is immediate peril from oedema the direction of treatment at the lowering of the pressure inside the cranium may more often allow the formation of a chronic abscess. Although the risk of rupture into a ventricle with generalization to the entire subarachnoid space still exists, in a fair number the ordinary inflammatory reaction around the abscess becomes reinforced by gliosis and completely encapsulated. During the process of spread from the outside focus to the brain, the arachnoid space has to be crossed, which may be achieved by a very narrow track indeed, a millimetre or so across, walled off from the general subarachnoid space by fibrinous adhesions; if these do not form, a diffuse meningitis is more likely to occur than abscess.

Tuberculosis

Direct spread to the meninges occurs from tuberculous osteitis of the spine and petrous bone, but far commoner is the blood-stream carriage of tubercle bacilli from sites elsewhere in the body. The type of inflammation excited in the brain is histologically and otherwise an exact counterpart of that elsewhere. Sizeable tuberculous masses known as *tuberculomata* may be found, but the important event is the infection of the subarachnoid space by the rupture of

any tuberculous focus, small or large, leading to *tuberculous meningitis*. That this does not develop directly from blood-borne infection of the meninges is shown by a great deal of evidence—it may come, without haematogenous tuberculosis, from rupture of a paravertebral tuberculous caseous mass into the meninges; the distribution of the meningeal tubercles is not that of a random blood-stream spread but follows the principles of gravity and the flow of the C.S.F.; experimentally it does not follow the injection of bacilli directly into the carotid artery of even a sensitive animal, but it always follows the injection of bacilli into the C.S.F. and often follows attempted surgical attacks on tuberculomata diagnosed as tumours.

The exudate in the meningitis is often unusually fibrinous, the disease frequently occurring clinically at the period of hypersensitivity in the patient, and this massive gelatinous exudate may collect around the base of the brain in such quantity that the tubercles are concealed: they can usually be seen clearly on the dorsum of the cerebellum and over the cerebral convexities. Although the earlier stages of the disease are directly due to tuberculous infection of the meninges, in the later weeks two other factors dominate the course—the impairment of the circulation of the C.S.F. by the exudate, a purely mechanical problem; and the impairment of the cerebral blood supply by *endarteritis* at the base of the brain; neither of these is at all controlled by anti-tuberculous drugs, which therefore must be given very early if they are to be effective. Actual destruction of the nerve tissue by the tuberculosis is a minor event, mainly concerning the oculo-motor nerves which have a long course through the exudate; infarction and cerebral compression from internal hydrocephalus terminated the illness in three weeks in the pre-streptomycin days.

Neurosyphilis

This involves the C.N.S. in two forms often mixed, *meningovascular syphilis*, a diffuse syphilitic fibrosis of the meninges and arteries with secondary damage to the nerve elements by reduction of their blood supply; and *syphilis centralis* in which the spirochaetes are present among and actually damage the neurones. The symptoms and signs caused depend on the distribution of the attacked neurones, whichever way they are attacked: the treatment of vascular syphilis used to be more effective than that of syphilis centralis; the outlook for neurones whose function was depressed by anoxia was better (when that anoxia was relieved) than the outlook for neurones in the presence of spirochaetes which were almost immune from attack inside the blood–brain barrier of the C.N.S.

PLATE 9. C.N.S. INFLAMMATION

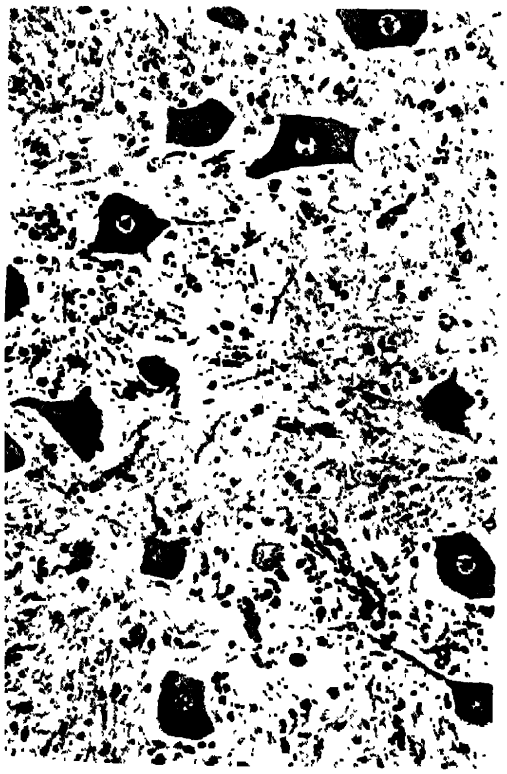
(*a*) Compound granular corpuscles in the wall of a chronic abscess. These large cells, with their foamy cytoplasm, are merely unusually conspicuous macrophages with ingested lipid material derived from the lipids of the myelin in particular. They have a round outline as they are in fluid at the edge of the abscess, and this is the reason for the presence of plasma cells among them. × 350.

(*b*) Perivascular " cuffing " in virus inflammation (anterior poliomyelitis). A dense accumulation of small mononuclear cells along the arteries of the spinal cord is conspicuous. The situation near the anterior horn cells makes it very likely to be due to poliomyelitis, but similar inflammation occurs in other infections, both of virus origin and syphilis and tuberculosis. The magnification is too low to give reliable information on the motor neurones. × 70.

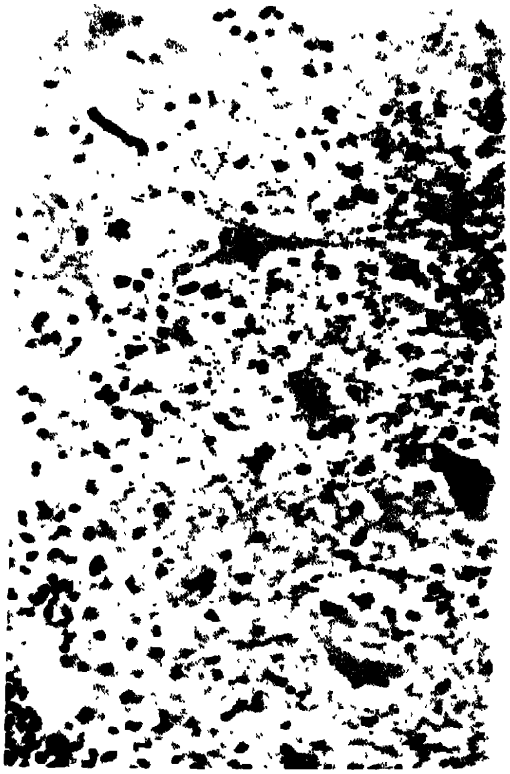
(*c*) (*d*) Normal and abnormal neurones. Those on the left have well-stained large nuclei with nucleoli; sharply outlined black dots of Nissl substance are present in most of them except in that part from which the axon arises. The cells without nuclei are not necessarily abnormal; the neurone is so large that a section may well cut the cell and miss the nucleus. But all the neurones in the right-hand field are abnormal; fading traces of nuclei are present in two, Nissl substance is absent from all; their outlines are becoming vague and rounded and glial nuclei are increased; in the bottom left is the edge of a perivascular accumulation of mononuclear cells (anterior poliomyelitis). × 140.

(*a*)

(*b*)

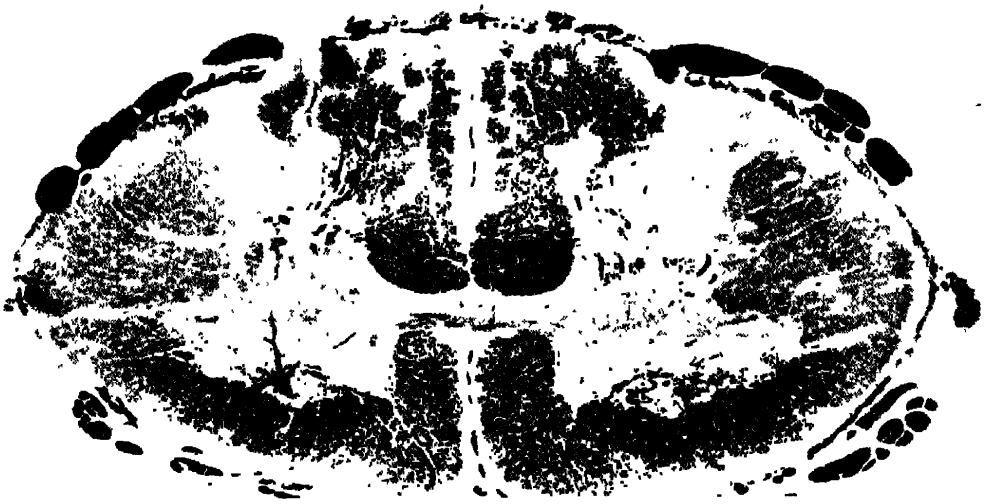


(*c*)



(*d*)

(*a*)



(*b*)

(*c*)

PLATE 10. DEMYELINATION

(*a*) Tabes dorsalis. Systematized demyelination of the posterior columns, consequent on the destruction of the posterior root ganglia by syphilis. × 9.
Weigert–Pal stain; normal myelin is black, the myelin of the posterior columns is missing, and the columns are shrunken and flattened.

(*b*) Perivascular demyelination: post-vaccinal encephalitis. The distribution of the loss of myelin here bears no relation to the tracts of the cord, but affects the periphery of the cord and the myelin along the penetrating vessels– seen best to the right of the mid-line; red cells (their phospholipid envelopes) stain black just as the myelin does, and the vessels can just be made out. Normal myelinated nerve roots outside the cord. × 9.

(*c*) Disseminated sclerosis. The medulla has three large irregular patches of demyelination, the biggest under the fourth ventricle spreading to involve the exit of the tenth nerve roots dorsal to the olive; the patch on the opposite side is just becoming confluent. An asymmetrical isolated patch involves the olive and pyramid. This demyelination has no relation to tract boundaries or to vessels, and has not the diffuse symmetrical picture found in degenerative processes due to known deficiencies or toxins. × 6.

Nowadays the treatment of both forms is vastly improved, but the dead neurone will still not regenerate.

Under the heading *syphilis centralis* the conditions *general paralysis of the insane* (*dementia paralytica*), *tabes dorsalis*, *primary optic atrophy* and the *Argyll–Robertson pupil* are included.

The distinction is not to be regarded as hard and fast, and combination of the two forms of attack is the rule rather than the reverse. The presence of the spirochaete has been proved in all clinical patterns; no more, however, is known of why any individual develops this form of syphilis, or where the spirochaete has been lurking and why it has become reactivated, than is known about the same points in syphilitic aortitis. Theories of special strains of spirochaete have been put forward, but none are capable of experimental proof.

Diffuse leptomeningitis of greater or less intensity, with infiltration of the Virchow–Robin spaces, accompanies the shrinkage of the cerebral convolutions in general paralysis. A somewhat similar atrophy in senile demented people may be distinguished by the greater intensity of the meningitis—no more than opacity in the non-syphilitic—but more certainly on the presence of iron in the cortex, demonstrable at autopsy, and histologically in the microglia at the site of the neuronophagia. Uneven loss of neurones, inflammatory cells, and gliosis in the grey matter are found; and a proliferation of the astrocytes under the ependyma of the ventricles and aqueduct of Sylvius forms granularity of the surface as seen at autopsy, and a similar gliosis round the aqueduct is the cause of the Argyll–Robertson pupil.

In tabes dorsalis the spirochaete is present in the posterior roots, but hard to demonstrate; the atrophy and subsequent gliosis of the posterior columns of the cord give the disease its name and most characteristic clinical and pathological feature. An intense inflammation round the optic nerve is found in primary optic atrophy; this disease and syphilitic aortitis are often associated with tabes.

Where the neurosyphilis is the result of congenital (transplacental) syphilis, the form taken is most often a mixed tabo-paresis.

Virus Infections of the Nervous System

These are common and important, and illustrate several points of general interest.

1. SOURCE AND ROUTE OF INFECTION. The delicacy of the virus and its dependence on cells to synthesize its requirements imply that the virus will not live long outside the body, and the contact in virus diseases is often conspicuous, as it is in *rabies* derived from

the bite of an animal suffering from the disease, and most present-day cases of *anterior poliomyelitis*. This was obscured in the past by the virus of poliomyelitis being carried in an intestinal phase without nerve-tissue involvement, the cases of paralysis being sporadic incidents in what was virtually an endemic harmless virus disease of the gut in infants. This change in the character of the virus disease illustrates that *diseases are going through evolutionary changes under our eyes*, and we must be on the watch for this in future. Another example of this change is in the disease *encephalitis lethargica*, an epidemic which spread widely in the 1920s and has since completely disappeared.

The route from the exterior to the nerve tissue is sometimes by way of the blood-stream (in many cases of poliomyelitis) but neural transmission is also found; the rabies virus travels slowly along nerve tissue to the brain, and by no other route; the incubation period thus varies with the distance from the bite to the brain—ten days in the face, two months in the leg. Neural transmission from the nerve endings in the gut is also possible in poliomyelitis, accounting for the frequency of involvement of the medulla in cases acquiring poliomyelitis after tonsillectomy; it is also demonstrable experimentally in the monkey.

2. SPECIFICITY OF THE CELL ATTACKED. Some of the virus diseases affect the skin or other tissues as well as the nerve tissue (zoster, mumps, varicella), others are strictly confined not merely to nerve tissue but to one set of cells in the nervous system, and this localization and the consequent symptoms make one of the easier ways of recognizing the viruses. Examples are the motor anterior horn cells of the spinal cord and their bulbar analogues attacked by poliomyelitis, the mid-brain and hippocampal localization of both rabies and encephalitis lethargica, and the posterior root ganglia attack of zoster.

More difficult to explain is the selection of some small group of these for colonization by the virus, e.g. one individual or two adjacent ganglia in zoster; accidental features of access or "exhaustion" of the group serving overworked muscles has been suggested for the sharply asymmetrical incidence of poliomyelitis.

3. FATE OF THE CELL AND THE INFLAMMATORY RESPONSE. The virus parasitizes the individual cell, which may die outright or may show the earlier changes of chromatolysis and degenerative rather than fatal changes. In rabies conspicuous inclusion bodies, the eosinophil cytoplasmic *Negri* bodies, are found, and similar bodies occur in inclusion encephalitis in the nucleus: no such bodies occur in poliomyelitis.

In a severe attack, neurone destruction may be severe enough to attract polymorphonuclear leucocytes, but in general the response is by macrophages and lymphocytes. These not only congregate around the affected cells but they are also found in the Virchow–Robin spaces of the arachnoid along the penetrating vessels. The presence of cells in this situation is an indication of a severe infection of the central nervous system, but it is not specific for any one infection, being found in tuberculosis and syphilis as well as in the virus infections mentioned here; distinction between the causative organisms is made on other factors in the inflammation and on the site favoured by the different viruses.

As far as the individual cell is concerned, it either dies and is not replaced at all functionally, though there is a slight glial scarring, or else it survives, throws off the invader and regains its normal histological features; chronicity of these infections has not been shown to occur.

Details of the antigenic structure and general virology of these viruses will be found in the companion volume on Bacteriology. Reference should also be made to the demyelinating diseases often miscalled encephalitis which follow some exanthemata and are discussed on p. 198 with the general question of demyelination.

Inflammation in Bone and Joints

Bone (Plate 8)

The principal features modifying the inflammatory response in bone are: (*a*) the calcified collagen which makes up so much of it is not easily removed, but requires the slow process of osteoclastic resorption; it mechanically impedes the processes of inflammation and drainage; (*b*) the tendency for new bone formation to occur as part of the fibrous reaction around the inflamed area. A safe generalization about bone pathology is that where in an ordinary tissue there is granulation tissue present in inflammation, in bone osteoclastic resorption also occurs; where fibrosis is normally expected, there new bone formation takes place. This new bone is of the special emergency type known as *woven* bone (Plate 8): this is not normally found after the first year of life, up to which time it is found in the formation of the membrane bones. It has the advantage that it can be formed without any preceding supporting tissue, whereas the normal bone of adult life, known as *lamellar* from the manner of its deposition, cannot be laid down except on a scaffolding which may consist of living or dead bone, cartilage (not necessarily only after removal of some of the cartilage) and occasionally on other substrates. It should be noted that these terms

" woven " and " lamellar " refer only to the microscopical structure of the bone; the naked-eye difference between the dense bone of the cortex (ivory corticalis) and the spongy medullary bone (cancellous) has no relation to this; both are lamellar.

ASEPTIC INJURIES. These are very common: the minor varieties, bruises or contusions, and the major, fractures. Fractures are further sub-divided into the *closed* or simple fracture, where the bony injury is entirely subcutaneous, and the *open* or compound fracture, exceedingly liable to become infected by communication with the outer world either directly through the skin or by an internal passage. The term " comminuted " refers to fractures in which there are several small bits, and " complicated " to those in which important structures other than the bone are involved; but in all ordinary examples it is to be noted that the lay term " a broken leg " is really more accurate than the apparently scientific " fractured tibia " since an injury severe enough to break the bone will also damage the soft tissues and muscles.

The first happening in fracture is that an extravasation of blood of greater or less extent will occur, coming mainly from the vascular periosteum, to a less extent from the marrow, and least of all from the ends of the cortical bone. The periosteum is only loosely attached to the surface of the bone, except at the muscular tendinous insertions, at epiphyseal lines, and at joint capsules, and is stripped from the surface for a variable extent on each side of the break; in this split the extravasated blood collects. The bone-forming cells of the periosteum are found on both sides of this cavity. The tough membrane called the periosteum consists mainly of fibrous tissue, with these cells on the inner surface; it is better to use the term for the whole tangible layer than to confine it to the thin layer of bone-forming cells alone, which do not make up a structure visible to the naked eye.

The normal processes of organization of this haematoma then proceed just as in other haematomata, and irrespective of whether the fracture is " set " or not. There will be little polymorph exudate as long as the fracture is sterile, but macrophages and granulation tissue appear, particularly around dead fragments of bone and jagged bone ends. With them osteoclastic activity begins, and during the first ten days this granulation tissue phase is dominant. At first, the jagged bone ends will mesh when brought into apposition: but later they become rounded off and the set bones will not engage so easily. Once the granulation tissue is in position, movement will dislodge the osteoclasts and other cells from their place of work: immobilization does not of itself unite the fracture and

heal it—it is the inflammatory process that does that; but immobilization does make the most economical use of the vascular supply.

A completely dead fragment of bone can take no part in the reaction. Pieces that have been completely separated from all other tissue, periosteum in particular, come into this category: although the calcified collagen is not alive, the cells that inhabit it are, and require an adequate supply of blood. If the piece is supplied by a fragment of vascular tissue only, it may remain alive, but unless the bone has a good blood supply it will not be able to support the active stages of the inflammation that will unite the fracture. Dead bone is not dissolved by either polymorph leucocytes or macrophages of the ordinary kind; if it is free in pus or fibrin it remains unchanged; the cells die and disappear but the irregular outline of the fragment is not rounded or softened; only osteoclasts supported by vascular granulation tissue can do that.

The second half of the healing process consists of the formation and ossification of fibrous but still very vascular granulation tissue. Though it is convenient to think of this as a second separate process, the two are continuous and overlap. In the early stages, migrant fibrocytes and capillary loops migrate out into the blood clot, and in the usual situation those coming from the opposite sides of the fracture meet and merge. Union is partly due to this, but partly due to general activation of osteoblasts throughout the area, both within the bone and much more extensively under the detached periosteum, detached well to either side of the fracture. On the foundation made by this granulation tissue woven bone fragments are built up, and replaced in their turn by the normal lamellar bone of the adult. This mass of ossifying fibrous tissue is referred to as *callus* (periosteal, the main mass; endosteal in the marrow, rather less; and interstitial between the bone ends, the quantities determined by the vascularity of the parts). Formation of callus is at its maximum about a month after the injury; its remodelling to an economical structure and one adjusted to the demands on the bone goes on for many years. The early callus is referred to as provisional, that finally formed as definitive.

Notice that the crossing and meshing of granulation tissue and fibrous tissue is only possible in the exudative stage of the fracture. Once the fibrous tissue becomes consolidated into sheets parallel to the plane of the fracture no amount of pressing the two together will make them fuse, even less so when the fibrous tissue is partly ossified or turned into cartilage. The only chance of fusion then is to start afresh with fresh granulation tissue after the sclerotic tissue is removed

Cartilage is not an essential part of callus though it may be often seen in it; the bone formation takes place directly from fibrous tissue and not by replacement of cartilage as in ossification of an epiphysis. Cartilage is more likely to be found in fractures where some mobility of the fragments is permitted, and as a fibro-cartilaginous plate between the ends of a long-standing un-united fracture.

DELAY IN HEALING OF A FRACTURE. Many causes are known, of which the most important is the *inadequacy of the blood supply*. This may be natural, due to the position of the fracture in an avascular area, to the line of fracture cutting off the blood supply of one fragment of the bone (e.g. the proximal half of a fractured scaphoid in the wrist or the sub-capital fracture of the neck of the femur); the head of the femur gets most of its blood from the retinacula at the upper side of the neck; the ligamentum teres is not sufficient to keep the whole head alive and maintain the inflammatory response; note the contrast in healing between this and the vascular transtrochanteric fracture. The slow healing of lower tibial fractures and the scaphoid of the wrist are easily understood. The poor blood supply may be the consequence of old age and arterial degeneration. Most practical, it may follow poor immobilization which allows continuous tearing and displacement of the components of the callus, especially in the early stages. Fractures in wild animals (e.g. deer, following deer-stalking rifle wounds) may be found completely healed without setting or immobilization of any sort, though usually in a bizarre position.

The second important cause is the *over-separation of the fragments*, usually from too enthusiastic traction. Impacted fractures usually unite well, where the gap to be crossed by the granulation tissue is minimal; as the gap widens, the granulation tissue sprouts lose impetus and instead of crossing the gap fall away and lie parallel to the fracture. If one side of the fracture is dead or nearly avascular, so that one side has to do all the healing, it is equivalent to doubling the gap. Unwanted tissue (e.g. muscle) may interpose between the bone ends also.

Imperfect immobilization produces its effects mainly by a combination of these two defects. The usually quoted example of healing in spite of poor immobilization is the rib fracture, but the attachments of the intercostal muscles and the way the chest moves mean that the play of the two ends on each other is limited, and in limb fractures poorly immobilized fractures are almost certain to end in false-joint formation. The natural muscular shortening that follows many fractures tends to impact and immobilize the break.

Sepsis is a most important factor. Whether it is a direct consequence

of the injury in open fractures, or gains access later either through natural channels in contact with the fracture (fractured pelvis and the urinary tract, fractured jaw and mouth), through surgical operations in setting the fracture, or possibly through blood-borne organisms settling in the clot, it results in the centre of the fracture becoming a purulent cavity instead of a fibrin mesh-work in which the fibroblasts can follow the scaffolding and unite with each other. For reasons which follow from the causes of chronicity (p. 54) once sepsis is installed in a bone it is extremely difficult to eradicate; it may be limited and union may occur but central persistence of the pus is usual. For these reasons primary amputation of badly infected open fractures, especially if there are large fragments of wholly detached, and therefore dead, bone, is often the quickest as well as the best treatment.

Lastly, *general diseases* may play a part. They can only be blamed if the surgeon is satisfied that the preceding points are satisfactory; it is no use making a positive Wassermann reaction an excuse for poor immobilization. Lack of calcium is not a cause of non-union even in severe calcium deficiency; the fracture heals by fibrous tissue, but does not then calcify until the calcium defect is put right. Giving excess calcium to a healthy man will not expedite the union of the fracture. The poor granulation tissue formed in scurvy, and the poor inflammatory tissue formed after cortisone and similar drugs are, however, real causes of non-union.

OPERATIVE MEASURES TO FIX FRACTURES. Two forms of support are used; metal plates and screws and bone, either living bone taken from other parts of the patient or dead sterilized bone from various sources.

Assuming complete sterility, metal plates and screws are encapsulated by chronic granulation tissue and fibrous tissue which ultimately ossifies in intimate relation with the metal. Metal phagocytosis by macrophages around is common, and unless the metal forming not only the screws and plates but also the screw-drivers is very carefully chosen electrolytic solution occurs after a time. The foreign body can be withdrawn if necessary as bone union will have taken place around it, but most remain in the patient for the rest of his life.

Grafts of living bone carry a few living cells on the surface, but the arterial supply of the interior is lost and it dies. This is less so when the bone fragments are small chips rather than grafts strong enough to give a structural value. Dead bone provides only a scaffolding, a natural one, which is relatively easily worked over by the bone cells of the part and finally replaced. This fate also awaits

living bone chips, but in this case the scaffolding carries a number of workmen.

PURULENT INFLAMMATION IN BONE (OSTEOMYELITIS). The routes of access are as usual the first thing to consider in inflammation of bones, as of internal organs generally. Injury (compound fracture) has been alluded to already; it is the most important cause. Blood-stream infection occurs, though uncommonly now; if skin cleanliness and antibiotic control of staphylococcal infections are lacking, as in the children of Great Britain up to 1939, it is common for infection to lodge in the metaphysis of a growing bone as a solitary pyaemic spread from a boil or infected graze.

When it does occur, bone infection is serious because all the requirements for chronicity are present; there is an abscess in a cavity with bony walls, which has no natural drainage, and which cannot collapse when drained surgically; there is dead bone in the area, and this material is full of crevices where organisms can persist.

Pent-up pus in the bone marrow causes both severe pain and toxic effects. Infected thrombus in the marrow venules was a potent source of pyaemia in the days when osteomyelitis was common. As far as the purulent inflammation went, there were few modifications; in the pus, the bone died, but remained otherwise unaltered; in the granulation tissue, the bone was often dead, but underwent osteoclastic resorption; in the outer fibrous tissue zone, bone deposition went on, usually taking the form of lamellar bone over the original living or dead trabeculae (Plate 3). The periosteal layer, as well as showing the fibrous tissue and plasma cell accumulations of a chronic purulent infection, was buttressed by a thick sheet (involucrum) of bone which enclosed the dead bone within (sequestrum) and discharged pus through sinuses to the skin. If the patient survived the acute attack and the risk of pyaemia, there was likely to be a long period of chronicity and relapse.

Spread from septic foci in the middle-ear and nasal sinuses may lead to osteomyelitis of the temporal and frontal bones of the skull as well as to infection within the skull, and bone can be infected from other adjacent infected foci.

TUBERCULOSIS. Again there is little modification in the primary response. Where bone trabeculae are involved in caseous material the bone cells die, but no solution of the calcified matrix occurs. In the narrow reaction zone, there may be traces of bone deposition, but as long as there is active infection in the area, there is a characteristic loss of density in the bone, possibly from disuse, possibly toxic, brought about by insufficient replacement of the normal bone removed in the ordinary turnover of this structure. This is of help

in deciding radiologically whether the infection is under control or not. The term " decalcification " usually applied to this process is undesirable in so far as it implies that the calcium is removed from the bone but its matrix otherwise left; this is not known to occur.

The site affected is often juxta-articular, and bone and joint may be hit apparently simultaneously; the spine is a favoured site. Parosteal caseous masses are frequent, tracking round the fascial planes to appear e.g. in the psoas under the inguinal ligament (psoas abscess) or along the ribs. The arterial supply to the spinal cord may suffer from pressure or endarteritis, leading to paraplegia, which is not in general due to the hunchback bony deformity that is so striking. When the tuberculosis is controlled healing by bone may occur and prove sound.

SYPHILIS. In the very young infant, before six months, a granulomatous and painful lesion at the epiphysis may be seen; the zone of ossification is wide and irregular. At other ages, the lesion of syphilis is a fibrous ossifying process, usually in the shaft of the bone or in a subcutaneous or submucous bone. These nodular deformities are the cause of the sabre-tibiae sometimes described. Gummata occur and, round the nose, may be rapidly destructive. The inflammation is true to type, but the generalization may be added that where there is fibrosis in another tissue, there is ossification in bone.

Inflammation in Joints

There are two big groups—those in which the joint is involved in ordinary inflammations which are found in other tissues, and those which are peculiar to joints. The latter is by far the more important and common; the rheumatic diseases may not be often fatal but they are disabling.

Simple Inflammations

TRAUMA. Joint cartilage being avascular cannot undergo any inflammatory response itself; the vascular synovial tissues can. Effusion of blood is absorbed in the usual way, but it is important that healing should not occur across the loose pockets of synovial membrane which the capsule requires to conform with the movements of flexion and extension. Shortening of these brings about " adhesions " that limit movement. The best guarantee that adhesions will not form in the organization of effusions is complete rest for the part.

Replacement of injured areas of cartilage is by fibrous tissue, which in the end may come to resemble cartilage very closely. Displaced fragments of cartilage may grow in the synovial fluid.

since the ordinary nutrition of cartilage is synovial, and act as loose bodies, checking the movements of the joint and keeping up a low-grade inflammation. This is much the most common source of loose body, but synovial fringes and osteophytes may also provide them.

PURULENT inflammation rapidly removes cartilage, which does not re-form. Vascular granulation tissue from the exposed bone may form adhesions with the capsule or with the opposite face of the joint if it too is eroded, and fusion of the joint by bone (bony ankylosis) is the result. Although septic arthritis is rare it is an urgent matter if the articular cartilage is to be preserved.

Less severe fibrino-purulent arthritis is known as a complication of dysentery, Reiter's non-specific urethritis, and gonorrhoea. If the cartilage is not destroyed, once the inflammation has subsided, restoration of function will be determined by the amount of fibrosis in the capsule.

TUBERCULOSIS affects joints and tendon-sheaths with an unusually fibrinous exudate overlying a typical caseous and granulomatous reaction in the synovial membrane, this fibrin appearing often in a compressed nodular form referred to as melon-seed bodies. The swelling is slow, white and painless, like tuberculosis elsewhere, and though bacilli may be found in the aspirate it is usually simpler and safer to look for tubercles in the related lymph-glands. Destruction of cartilage is less rapid and complete than in purulent arthritis, because the cartilage is not invaded but separated from the bone by a slow granulomatous dissection, and quite large fragments may be encountered. As before, after healing there is no regeneration of cartilage, and more or less complete ankylosis is the usual result.

Special Inflammations

" Rheumatic joint disease." Two of these, rheumatoid and osteoarthritis, are very important diseases.

RHEUMATOID ARTHRITIS is a general disease with the main burden on the joints. It occurs in two forms: (*a*) that of classical rheumatoid arthritis in young women, and (*b*) what is sometimes called " toxic " arthritis in people of either sex and any age; the joints affected are less uniformly symmetrical, and often the larger joints. In the classical disease, the patients are ill in themselves, anaemic, achlorhydric; they lose weight, show a raised sedimentation rate, and often a low fever. The lymph-nodes and spleen may be enlarged, with a non-specific macrophage hyperplasia. Subcutaneous nodules are found in which the collagen is infiltrated with a fibrin-like substance (fibrinoid necrosis); lymphocytic infiltration of the wasted muscles and skeletal atrophy are usual.

The joints involved are primarily the smaller distal joints of the hands and feet, spreading up to the wrists, elbows, knees; the larger joints may be affected, but when they are, the patients are often older, male, and only one or two joints may be concerned. In the early stages, an inflammatory thickening of the capsule and synovial membrane is found, leading to stiffness and to swollen thickened joints, but in this stage no permanent damage has been done. The synovial membrane characteristically has nodules of lymphocytes and plasma cells around the vessels. This synovial granulation tissue spreads over the cartilage from the margin (pannus) coming between the cartilage and its natural source of nutrition in the synovial fluid, and eroding it; similar tissue is present in the subchondral bone. This destruction of the bone-ends results in dislocation of the joint, and in fibrous ankylosis between the surfaces. The disease may burn itself out, leaving fibrous tissue in place of the cartilage; as before, there is no regeneration.

The resemblance to rheumatic fever lies mainly in the change in the collagen, notably in the subcutis over pressure points, where similar nodules occur in both diseases. The arthritis of rheumatic fever is an acute transient one; subacute cardiac lesions are however rather more common in sufferers from rheumatoid arthritis than in other patients.

We have little to go on in deciding the cause. The histology is undoubtedly inflammatory, though polymorphs are few; plasma cells are conspicuous; the antigen–antibody mechanism is clearly being put into effect, but there have never been successful cultures of micro-organisms. The possibility that it was a toxic response due to "focal sepsis" was thoroughly explored in the 1920s; every detachable organ which could possibly hold an infection, from the teeth and tonsils to the appendix and gall-bladder, was removed, without altering the course of the disease. Throat infections were a possible cause just as they are in rheumatic fever, but the tonsil is not the only lymphoid tissue in the pharynx and disappointing results have followed its removal in both diseases. The similarity with rheumatic fever is close, in that very similar nodules may be found in the subcutis in both diseases. The modern variation of the "septic focus" theory, an allergic response at a distance, may be true; antigenic similarities between the polysaccharides of connective tissue and those of certain streptococci have been shown, but the disease has not been reproduced in animals though a remarkable close resemblance in the joint inflammation produced in pigs by *Erysipelothrix rhusiopathiae* has been found.

OSTEOARTHRITIS is an extremely common process, affecting larger

joints more, and not associated with any general disability. Although the name suggests an inflammation, there are no histological features such as suggest an inflammatory origin for rheumatoid arthritis. Changes take place in the cartilage with no cells present other than those in the cartilage, which sometimes multiply and sometimes become fewer, but always produce a different type of matrix; this is less effective in carrying out its function of elasticity, and splits into fragments generally vertical to the surface. This process begins in the middle of the joint, and goes on until the underlying bone is exposed, having thickened to meet the extra strain. At the same time ossification invades the border of the joint surface forming rounded knobs (osteophytes) which may prevent full movement of the joint in one direction or may get broken off and form a loose body. Complete erosion of the cartilage and polishing of the thickened bony surface is not uncommon in the knee or other joints. There is no granulation tissue, and ankylosis does not occur.

The title " degeneration " is applied to processes of this sort, but though it correctly states that the cartilage is not so good as it was before it does not either describe the inadequacy nor explain how it occurs. Trauma undoubtedly plays a part in aggravating it even if it is not the original cause; the affection is commoner in overused joints or in those which are mal-aligned, and it is more related to friction than to direct pressure. Some synovial reaction occurs later in the disease, but there is no interference with synovial nutrition nor invasion of the cartilage by pannus. It is really out of place in the inflammatory section of this book, but it is convenient to put it beside the other joint diseases if only for contrast. The patients often do not complain of it, but severe examples usually come to the orthopaedic surgeon (osteoarthritis of the hip or morbus coxae senilis, that of the great toe joint—hallux rigidus and hallux valgus, that of the patella; chondromalacia is the name given to the earliest stages) for treatment of the particular local joint which is giving pain or limiting movement. Tendons and intra-articular ligaments may be ruptured by attrition against osteophytes.

The curious arthritis known as *Charcot's disease* is best regarded at present as a very florid example of osteoarthritic erosion of both cartilage and underlying bone, with osteoarthritic osteophytes, occurring in a joint which has become painless from neurological disease —syringomyelia, diabetic neuritis, tabes dorsalis; overstretching of the joint due to loss of proprioceptive sensation is the rather unconvincing reason given for the gross destruction, in the absence of proof that there is a trophic function in the nerves concerned.

ANKYLOSING SPONDYLITIS is again a general disease, but unlike rheumatoid arthritis it affects men rather than women, in young adult life, and the joints involved primarily are those between the vertebral articular processes (not intervertebral discs) and the sacroiliac joints, spreading to the hips rather rarely, and even more rarely to the distal joints. As the name suggests, the end result is the complete disappearance of the cartilage on both faces of the joint as the result of ossification. In the synovial membrane, in the early stages, an inflammation rather like rheumatoid is seen, but in spite of the view held (notably in America) that this is simply a variant of rheumatoid arthritis, the differences seem greater than the similarities.

GOUT is a general metabolic disorder of purine metabolism in which excess of urate is deposited in the cartilage both of joints and of the pinna; the mere level of the uric acid in the blood though high is not enough to cause the disease, which can reach greater heights in nephritis and leukaemia without precipitating into the joints. The reaction to the precipitate is acute inflammation; recurrent attacks are characteristic and deposits in the kidney may lead to death from uraemia. As in many general metabolic disorders there is often a family history suggesting genetic abnormality.

Radiations

It would be ideal to take this important source of danger in detail, considering the effect of each kind on the different components of cell structure, and on individual cells studied in tissue culture, and deduce from that what effects might be expected in the intact body; however, this is too elaborate for the space available.

1. ULTRA-VIOLET LIGHT. This short-wave light has limited penetration, thinned out in many climates by cloud or smoke, and is stopped by about 1 mm thickness of tissue. The melanin granules found in the basal cells of the epidermis on the surface side of the nucleus have a further protective effect in shielding the nucleus, and are conspicuously increased if there is intense U.V. light irradiation either in tropical climates or following therapeutic exposure. The damage that is none the less done to the nuclei is seen in the increased frequency of neoplasms and atrophies of the skin in white populations unduly exposed to U.V. light. With added thermal effects, an acute U.V. light reaction is seen in sunburn; after a short latent period, about 6-24 hr, a sharp inflammatory reaction takes place in the skin with erythema, blistering and peeling; subsequently the melanin is increased.

2. IONIZING RADIATIONS. These include both the natural risk from

penetrating radiation (cosmic rays) and naturally occurring radioactive sources, and the increasing quantities liberated by science, industry, and medicine; the total is immensely increased by warfare with atomic weapons, and increased to a debatable amount by the preparations for such warfare.

The sources may be conveniently classified as—

(*a*) Local Exposure. Therapeutic and diagnostic radiology. The radiation is limited in amount, the wavelength controlled, the area exposed sharply circumscribed.

(*b*) Accidental General Exposure. Work in scientific diagnostic and radiological departments; exposure to atomic warfare.

(*c*) Internal Radiation. Administration of radioactive materials for diagnosis or therapy; contamination of food and water by the fall-out from atomic explosions. The importance of this group is that whereas in the first two groups the effects of alpha- and beta-radiation can be ignored because of their poor penetration, they cannot be ignored in internal exposure.

Three general points are applicable. The dosage is cumulative; minor repeated exposure is therefore as dangerous as a gross accidental single exposure. The penetration varies, but is considerable; internal organs are accessible, and the screening value of protective measures, though accurately enough known physically, does not give certain protection. Lastly, there is a considerable period of latency before the effects show up, from days to years.

The effects produced are dependent in detail on the effects of the radiations on the atomic nuclei they encounter. They can dislodge electrons, so activating ions; they can produce hydrogen peroxide from water; they can be stopped by and injure the aromatic amino-acids of proteins in particular, and so the nucleo-proteins are particularly liable to be hit.

Four groups of cells are particularly sensitive to these rays, though in sufficient dosage any cell in the body can be killed by them. These special target tissues are: (i) the lymphocytes; (ii) the bone marrow; (iii) the germ cells of the ovary and testis; and (iv) any cell undergoing mitosis—this last is at the back of the treatment of malignant growths by irradiation; the cells therein undergo mitosis frequently and may prove unusually susceptible to irradiation for this and other reasons; some growths are so sensitive that the growth can be killed while leaving the adjoining tissues unharmed but others are so resistant that death of the growth can be obtained only at the cost of severe damage to the surroundings. The effects of the irradiation may be considered under three heads—

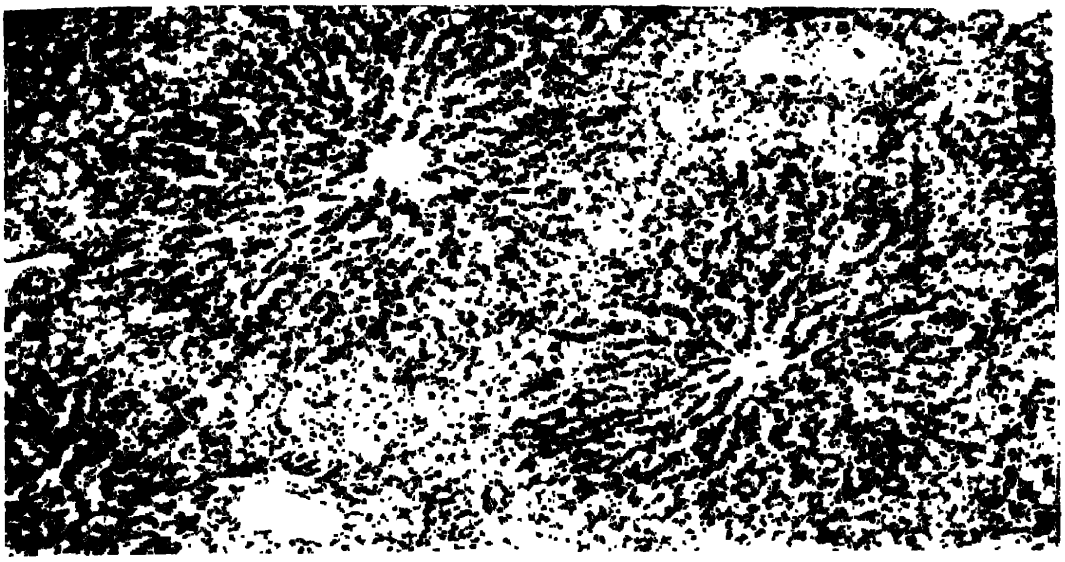
PLATE 11. LIVER

(*a*) and (*b*) Zonal fatty degeneration. In these two plates, some of the liver cells in the lobules have become infiltrated with fat, brought from the depot fat, this material cannot now be metabolized because of the derangement of liver cell function by toxic agents. There is no necrosis of liver cells and no accumulation of blood in the centres of the lobules. × 80.

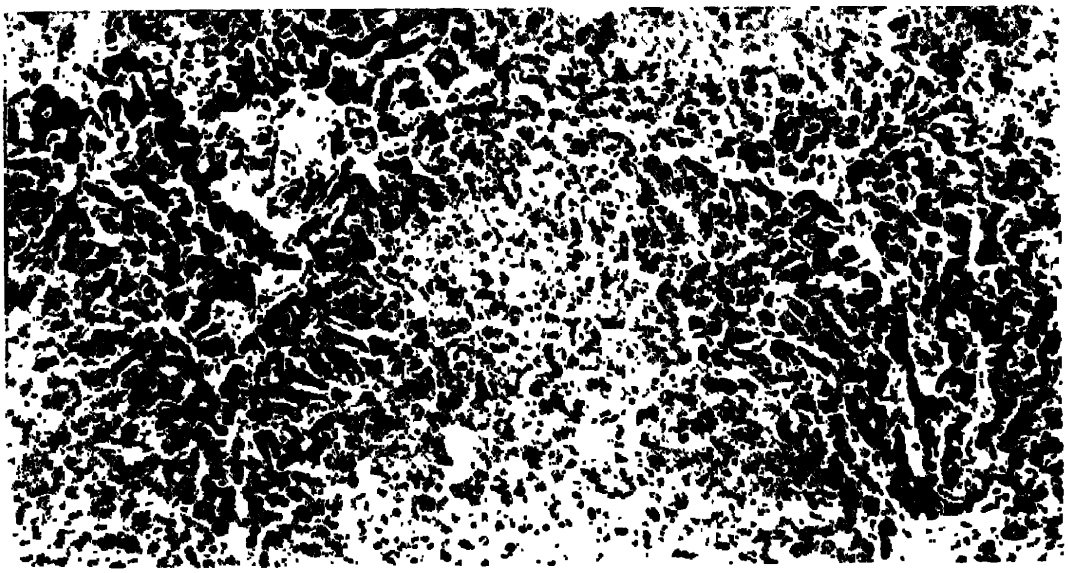
In (*a*) the pale areas lie around the liver lobules and include the portal tracts; the dark normal liver columns radiate from the central hepatic veins. This is therefore a peripheral or portal zonal degeneration. The fat is present in the usual form of large droplets displacing the hepatic nuclei.

In (*b*) the pale areas are centrilobular—a conspicuous hepatic vein near the middle of the lower area; the healthy liver cells include the portal tracts. This is the commonest kind of zonal damage. The fat in this example is in the less usual form of fine droplets which distend the cells but do not displace the nuclei.

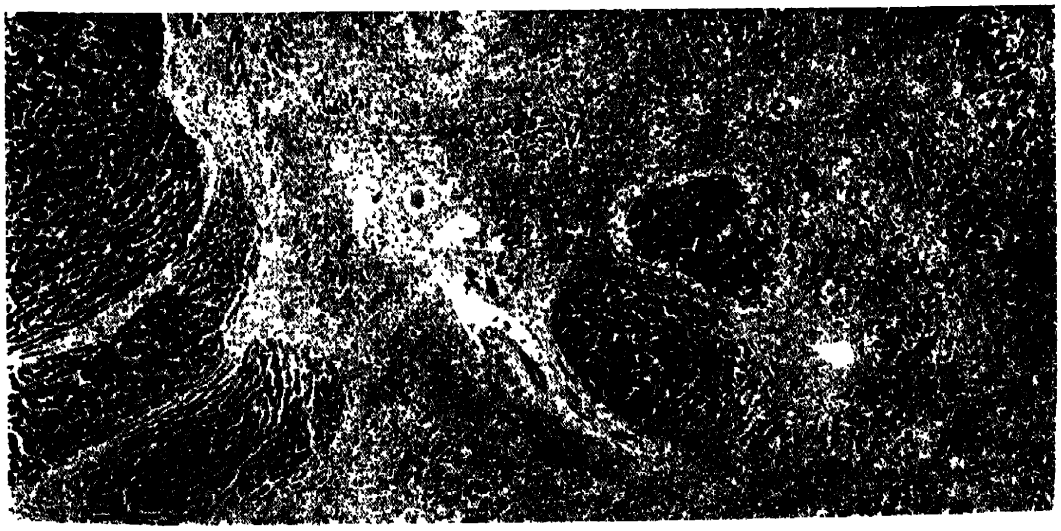
(*c*) Early regeneration nodules of cirrhosis. Following subtotal destruction of this area of the liver, isolated surviving cells have proliferated to form nodules of varying size, which are not organized as normal lobules with central veins. Between them is much fibrous tissue with inflammatory cells; portal tracts can be seen which show that this represents the site of many original lobules; the new nodules bear no relation to the old lobules. The connective tissue supporting the destroyed area has collapsed and become concentrated by the loss of the secretory cells, but many small groups of proliferating cells can be seen, sometimes forming tubule-like structures (" pseudo-bile canaliculi "), e.g. near upper left. × 25.



(*a*)



(*b*)



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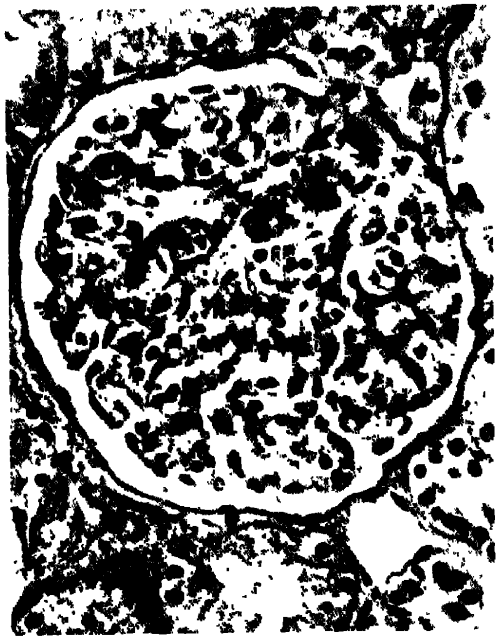
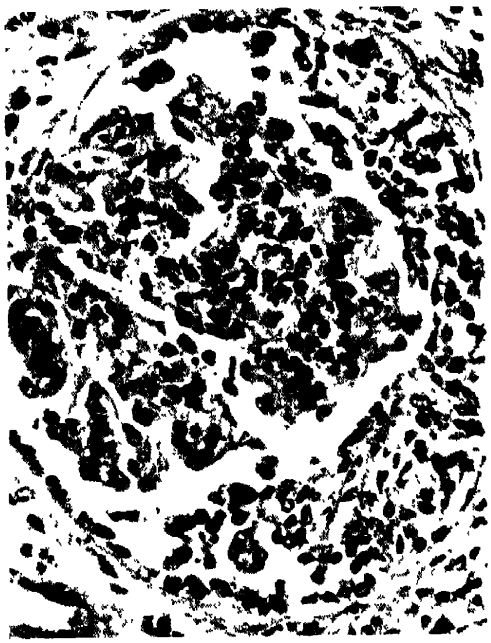
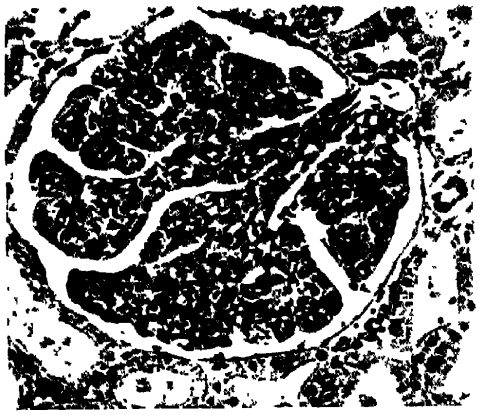


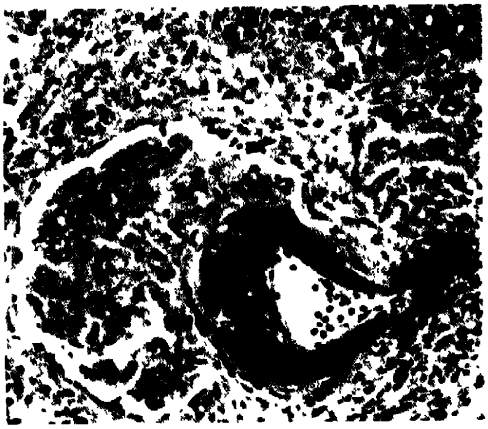
(*a*)



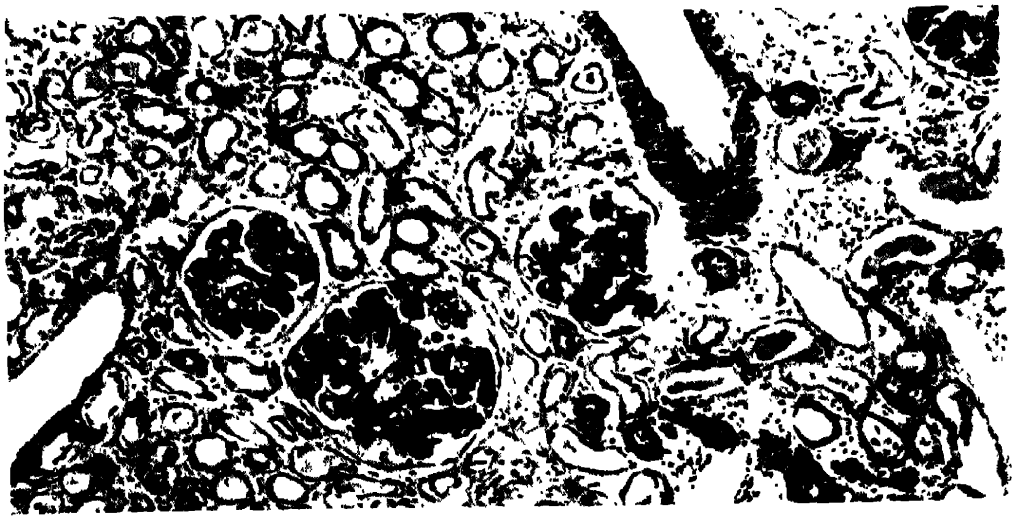
(*b*)



(*c*)



(*d*)



(*e*)

PLATE 12. KIDNEY

Glomerular changes are usually the most conspicuous and should be studied first; but the tubules should not be overlooked, though there is no room to include pictures of them.

(*a*) Normal glomerulus and adjacent convoluted tubules. No fibrous tissue; nuclei of epithelium and capillaries of the tuft spaced out, as are those of Bowman's capsule; tuft in a single mass; basement membrane not conspicuous. × 230.

(*b*) " Crescent " formation in nephritis. Proliferation of the epithelium of Bowman's capsule in response to unknown stimuli. Some fibrosis around the capsule; the tuft is compressed and contains more nuclei than normal. × 230.

(*c*) Proliferative glomerulitis in early acute haemorrhagic (type I) nephritis. The glomerulus is larger than normal and is packed with nuclei but there is no proliferation of Bowman's capsule. No fibrosis in the area at this stage of the disease; the tubules have normal cells but protein material in the lumen. × 130.

(*d*) Fibrinoid necrosis of afferent arteriole in malignant hypertension. Destruction of the wall and swelling of the vessel because of infiltration with a material resembling fibrin. The glomerulus in this example is not destroyed because there is still a lumen in the artery, but usually haemorrhage or infarction of it is seen. Inflammatory cells round the artery. × 130.

(*e*) Amyloid deposition. × 80. The glomeruli are infiltrated with dark masses of acellular material; the position of the abnormal substance outside the cells is better seen in the rings in which it is laid down round the tubules in the upper part of the field between the glomeruli and the artery. It is also present in the walls of small blood-vessels, e.g. near bottom right.

1. THE CELLS ACTUALLY HIT. These may be killed outright; they may lose their special functions so that they merely exist without secreting their products; they may show nuclear fragmentation; mitosis may be completely arrested or may be abnormal. Even when no structural change can be seen in the cells, the presence of severe damage may be seen in their descendants; the chromosomes may be so altered that the new cells are abnormal. Two major sequels are likely; in the individual, the damaged cells may develop the form of growth that is known as cancerous—an uncontrolled proliferation that proves fatal; in the race, the abnormal sex cells may lead to defective future generations. This transmission of damage far beyond the individual lifetime is the major hazard of atomic warfare.

2. THE INFLAMMATORY RESPONSE. The blood-vessels, particularly the small arterioles and capillaries, show dilatation followed by endothelial damage, the wall becoming thickened by fibrin, and the lumen narrowed. The dependence of the whole process of inflammation on a sound blood supply has been emphasized, and here the whole area of small vessels is threatened. As a result, the healing of irradiated areas is slow; surgical incisions cannot be made in them; the dead tissue is slowly removed; granulation tissue may be indefinitely delayed. Ulcers following irradiation may thus be as difficult to heal as the growth whose destruction caused them; they do not spread, but unfortunately they may be very painful.

Collagen is disrupted, though often there is a considerable excess of it laid down. The fragmentation of elastic tissue is conspicuous in the subcutis; the source of this elastic is so inadequately studied (like elastic tissue in general) that nothing can be said about it.

3. RECOVERY AND REPAIR. Tissue cultures may recover from irradiation if immediately washed, suggesting the damage may be partly due to toxins liberated from the damaged cells.

Morphological changes in the cells are usual, both in the fibrocytes and the epithelial cells. The apparently uninjured neighbours which move in and make good the loss may do so efficiently, leaving perhaps only slight pigmentation and atrophy of the skin, but with histological changes. The incompleteness of this healing may be latent for decades, until many years after exposure the skin develops multiple cancerous areas.

In general, it may be said in summary, that where there are unaffected cells in the surroundings they may heal the burn, though much hampered by the vascular and fibrocyte damage; partially affected cells may make a temporary repair, liable to breakdown later because of delayed genetic damage to the cell nuclei; and that the badly hit cells will die, fairly quickly.

Cortisone and Allied Drugs

Until comparatively recently the medical profession could do very little to modify the inflammatory response; their therapeutic efforts were in general directed to assisting it by various means—local heat, rest, the mild anti-inflammatory salicylates with their more important effect on the pain of inflammation; the direction of research was antibacterial, though it had long been recognized that antibacterial drugs will not be effective if they upset the body's own defensive mechanisms; this determined the move away from Listerian antisepsis to asepsis. In the earlier stages then therapy was concerned with minimizing the amount of inflammation necessary, in the later with the liberation of pus if any accumulated.

This unsatisfactory position was challenged first by Domagk with the sulphonamides in 1935, and a few years later by penicillin, and since 1945 by a flood of antibacterial substances loosely called antibiotics since many are derived from living organisms. For their actions you are referred to the companion volume on Bacteriology. They do not directly affect the process of inflammation except by diminishing the bacteria which cause it. A few years later in 1949 Hench followed up the clinical observation on rheumatoid arthritis, that clinical remission sometimes accompanied pregnancy, by research on the adreno-cortical steroids that led to the discovery of cortisone, which with its allies gives the medical profession a control of the inflammatory process—a great power for better or worse. It is entirely a negative control; that is to say its use as a drug leads to the depression of inflammation; there is no drug yet known which will increase inflammation in a patient who does not show a natural inflammatory response. We now have, therefore, a drug which can be used to suppress inflammation when the process is unnecessary or harmful, but which will have as one of its side-effects the suppression of inflammatory reactions which may be very necessary; the use of cortisone in patients with smouldering infection, e.g. gastric ulceration, is therefore potentially dangerous. There are other side-effects of very great importance, usually undesirable, which derive from the endocrine character of this drug, and are dealt with later in the chapter on the suprarenal cortex (p. 204); these are less in the newer preparations.

The suppressive effect of cortisone is exercised on all the stages in the inflammatory response; the action is apparently directly on the cells. In the *exudative* stage, the permeability of the capillary walls is reduced, so that inflammatory exudates and oedema are much lessened. The vascular dilatation is similarly affected; both the

phagocytic cells and the non-phagocytic are depressed in number and activity. In the *granulation* stages cell-division is held back (this may be direct action on the cell or it may be secondary to vascular changes) both in the granulation tissue proper where there are fewer fibrocytes and capillaries, and in the epithelium which is required to grow over the wound.

This action of cortisone is not dependent on the cause of the inflammation, nor does it alter the primary responses of the inflamed part—its effect is entirely quantitative and non-specific. Where the inflammation is necessary for healing, e.g. fractures, it has no place. Where the inflammatory process is contributing to the disease, as in many diseases due to auto-sensitization or hypersensitivity, it may be used with great success to damp down the unnecessary effects; it is thus found in the treatment of polyarteritis nodosa (p. 97), rheumatoid arthritis (p. 113) and severe allergic manifestations. Where powerful antibacterial agents can take over from the body the control of bacterial growth better than the inflammatory process itself, cortisone may suppress these inflammatory reactions and permit better access for the antibiotic—a new dramatic use of a powerful weapon that is under trial in tuberculosis. But it cannot be directed against one infection in a human body that is attacked by several, and the amount which is necessary to produce good anti-inflammatory effects may be very close to the dosage that is troublesome endocrinologically. Adrenocorticotrophic hormone is similar in effect but acts through the subject's own adrenal glands. Further, since at the end of any inflammation there must come a time when the repair of the damage is required, the depressant effects of cortisone may again be quite out of place. Although hailed as a life-saving introduction, the very power of this drug marks it out as likely to have powerful dangers, and the indications for its use have become narrowed rather than extended with use. It has obvious value as a diagnostic and experimental tool, and has been a pioneer introducing the idea of interfering with and actually suppressing the body's own most effective defence process, which would have been absurd to doctors twenty years ago when there were no antibiotics to stand between any such attempts and disaster from bacterial invasion. The century-old discovery of anaesthesia and antisepsis, each of which enhanced the value of the other, is paralleled today in antibiotics and anti-inflammatory drugs.

Amyloidosis

Following prolonged suppuration, particularly chronic osteomyelitis and bronchiectasis, patients were found to die of renal failure;

after death enlargement of the liver, spleen and kidneys was found which was due to an intercellular deposition of a material which stained brown with iodine. It was called *amyloid* from a resemblance in this to starch and the name has stuck, though inaccurate. The material is a glycoprotein containing a chondroitin–sulphuric acid and a globulin; the chemical composition is not constant, in different cases, and amyloid represents a group of substances. Although the historic dark-brown staining with iodine is still of value in the necropsy, a more precise reagent to demonstrate its presence is the dye Congo Red, which stains amyloid salmon-pink. This is so strongly adsorbed to the amyloid that it can be used to demonstrate the presence of amyloid in the living patient; an intravenous injection of the harmless dye is cleared out of the blood by amyloid, if present, in a time in which the normal patient hardly excretes any of the dye.

The association of this material with chronic inflammation, in which there is a rise in the antibody globulins in the blood, was matched by its appearance in the horses in which diphtheria antitoxin was prepared, in which the antibody-response was deliberately stimulated for a long time. It also appears in other patients with hyperglobulinaemia, notably those with the neoplastic growth of plasma cells known as myelomatosis (p. 243); the association of plasma cells and globulin antibody has been shown. It may therefore be held that the appearance of this material is due to the precipitation of serum globulin along with other substances in conditions of hyperglobulinaemia, of which chronic infections are the commonest. Apart from the two mentioned above, rheumatoid arthritis, tuberculosis, particularly that of bone and joint, and gummatous syphilis are notable as causes; leprosy, Hodgkin's disease, actinomycosis, and many infections and chronic ulcerations have been found to cause it. It is rather easily overlooked (both clinically and pathologically) and should be specifically searched for in patients with any prolonged infection.

The material is deposited in the basement membranes of the glands and spleen. Clinically the most important place is the *kidney* (Plate 12) where it is found in the basement membranes of the glomeruli, the tubules and the blood-vessels. At first this leads to swelling of the organ, and an unusual leak of protein through the urine; later the kidney becomes fibrous and the patient uraemic and hypertensive. This is how the condition proves fatal. The *liver* is usually severely involved, the material lying along the mid-zones of the columns to begin with, spreading to the centre, and leaving only a few healthy cells around the portal tracts; the cells disappear as a simple atrophy, presumably due to the precipitation of this

material between them and their blood supply. In the *spleen* the deposits occur either as isolated nodules in the Malpighian bodies ("sago spleen," from the translucent granules against the dark background) or as streaks along the walls of the splenic sinuses, giving considerable enlargement. Adrenals and thyroid may also be conspicuously affected. The organs concerned are hard, heavy, and show clearly the anatomical details of their shape, as if distended with this material; they are somewhat translucent on section—hence the alternative name sometimes used, "waxy" or "lardaceous" degeneration. The disease is not strictly a degeneration, though the adjacent cells undergo atrophy because of the presence of the substance. It is removed slowly if the cause can be removed.

This kind of amyloidosis is known as typical or secondary since it follows an infection. Rarely, a similar material is deposited in the heart and smooth muscle generally; this is called primary or atypical amylosis, for which no cause is known.

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CHAPTER 5

MECHANICAL BREAKDOWN OF TRANSPORT WITHIN THE BODY

THE separation of functions which are performed by a single-celled organism into those performed by the several organs of the body implies the development of a transport system to supply these organs with essential requirements and remove the products of their metabolism. The processes of diffusion and the exchanges taking place at the cell-surface are no longer adequate in themselves, though they still obtain in the individual cells of which the organs are composed, and in the tissue fluids intermediate between the blood and the cells.

Each organ, therefore, must have a blood supply and drainage, and many of them ducts for the removal of their products, which (as far as the cell that makes them is concerned) are excretions, but if the body has some use for them are referred to as secretions. Further, the alimentary tract must be capable of handling a steady flow of food and water.

The essential thing behind all this transport is muscular power. The heart and blood-vessels, the alimentary tract, the ureters and bladder, the uterus, all are obviously muscular organs; the travel of duct secretions is sometimes a matter of secretory pressure, but in the breast is driven by the myoepithelium. Although failure of transport from muscular failure is possible, the efficiency of the muscle is great enough to make this the rarest of causes, and failure of transport in the body is nearly always the fault of structural blockage to the passage and not to lack of a driving force. Secondary changes destroying the muscle are, however, often important in preventing restoration of the flow.

Certain generalizations are common to every transport mechanism in the body. (*a*) The causes of blockage can be conveniently considered under the three heads: those occurring in the lumen, in the wall, and outside the wall pressing on it. (*b*) Wherever there is obstruction there will be dilatation proximal to it, followed by hypertrophy of the muscle responsible for passage through the block, e.g. the colon proximal to a carcinoma, left atrial hypertrophy when

the mitral valve is narrowed. (*c*) If bacterial access is possible, a stagnant tube will become infected, and conversely unless there is stagnation it is almost impossible for an infection to be established in a flow.

OBSTRUCTION TO THE BLOOD SYSTEM

Blood-vessels

By far the most immediately dangerous of stoppages are those occurring in blood-vessels and they will be considered first. Although the shortage will include substances other than oxygen, oxygen lack is felt so much more rapidly than any other need that in effect the results are determined by the shortage of oxygen in the affected part. The anoxias arising from stoppage of blood are local effects; this condition of shortage of blood-supply is referred to as " ischaemia," the term having to be used for absence of oxygenated blood, since the term anaemia has another connotation.

If there is a blood system, it is essential that there should be a mechanism which will prevent the loss of blood from trauma. It is equally important to have a mechanism which will prevent the clotting of blood in the vessels, either spontaneously, or when a clotting mechanism has been set in motion locally to prevent blood loss.

1. Arrest of Bleeding

Two sets of events are concerned—the coagulation of the blood, and the behaviour of the capillary walls or those of arteries and veins; platelets are concerned in both reactions.

(*a*) COAGULATION OF THE BLOOD. The clot is made of *fibrin* derived from the plasma protein *fibrinogen* very rapidly under the influence of the enzyme *thrombin.* This rapid step is faulty only in the absence of fibrinogen, which may result from hepatic disease, and may occur *post-partum*, but is very uncommon.

The formation of the thrombin is much more complex, much slower, and much more can go wrong. The precursor is *prothrombin* also made in the liver, but only when there is adequate vitamin K in the gut, for this is largely synthesized by intestinal organisms. The necessary enzyme for the conversion of prothrombin into thrombin is *thromboplastin* (thrombokinase), itself activated by a thromboplastogenase, liberated by platelets when they are damaged or come in contact with a wettable or rough surface. Four other plasma factors are necessary, in order of their action: anti-haemophilic globulin (whose absence is the cause of haemophilia); a similar substance known as " Christmas " factor at present; and

factors known by the numbers V and VII; calcium ions are also required, these being always adequate in life though citrate (which combines with them) and oxalate (which precipitates them) are used to keep blood fluid when it is drawn for transfusion or analysis. Thromboplastins are also available from normal or damaged tissue, and can be extracted for laboratory estimations conveniently from brain tissue. Both phospholipids (lecithin and cephalin) and lipoproteins have thromboplastic action, and a further source is the action of thrombin on platelets. The reaction is thus self-propagating once traces of thrombin are formed by the disintegration of a few platelets.

The formation of thrombin from prothrombin takes about 10 sec.; this time forms a convenient estimate of the coagulability of the blood when the defect is in this part of the reaction. The slow generation time of thromboplastin can be measured. The crude overall efficiency of the whole process is measured by the coagulation time of whole blood—normally about 5-10 min. in venous blood.

Natural disease of this system includes the genetically determined absence of anti-haemophilic globulin and "Christmas" factor; deficiency of vitamin K and fibrinogen in liver disease; but never calcium lack, since the lowest blood-calcium levels are adequate. More important than the natural disease is the use of anti-coagulant drugs—salicylates, and the dicoumarol group of drugs (which are metabolized to salicylates); these have a slow-developing but prolonged action on factor VII and so on prothrombin formation. Heparin has a more immediate and shorter action on all the globulins involved in the process, easily reversible by protamine. The poison of viperine snakes is a potent thromboplastin; that of the cobra tribe on the other hand contains an anti-coagulant as well as a neurotoxin, and other toxins; the leech produces an anti-thrombin (hirudin).

Apart from viper bite, excess of coagulants has not been reported as a cause of general disease, though local clotting (thrombosis) is responsible for far more disease than excessive bleeding.

(*b*) VASCULAR FACTORS concerned in the arrest of bleeding. Contractility of the vessel wall is conspicuous in arterial damage, present and important in capillary breaches, but of little importance in veins. Minor breaches which are not closed by the endothelial cells are sealed by platelet thrombi. The bleeding which results from defects in these takes the form known as *purpura*—multiple small haemorrhages, not related to gross trauma, sometimes confluent to form larger patches known as *ecchymoses*; multiple fine haemorrhages are not seen in defects of coagulation.

Evidence of failure is provided by the estimation of the time taken by a simple prick to cease bleeding (the bleeding time, distinct from the clotting time); by the counting of the platelets; and by the placing of a venous tourniquet on the arm, congesting the capillaries and bringing out any weakness in their wall by the appearance of purpura in the forearm. These help the primary division of the causes of purpura into:

(i) Thrombopenic, where the fault is in the platelets. Deficient formation of platelets in the marrow—aplastic anaemia, acute leukaemia; primary thrombopenia, where the defect may be poor formation or excessive splenic destruction—probably the latter, since splenectomy often corrects the bleeding with dramatic suddenness.

(ii) Capillary wall defects with normal platelets. Deficiency in vitamin C (scurvy); infections with meningococci and the typhus group of fevers (p. 50); and ill-understood allergic and anaphylactoid states with heparin in the blood-stream in excess, and histamine as well; there may be an associated coagulation defect in this group.

There are two further ways in which the platelets may secure haemostasis; they are believed to liberate a constrictor substance, *serotonin*; and they are known to be associated with the retraction of the blood clot. Although in a tube with rigid walls this relieves the obstruction, this will not occur in a soft tissue in which the fibrin strands are attached to the walls.

2. Prevention of Clotting

It is possible to arrest the process of clotting when blood loss is controlled.

Circulating antithrombin and fibrinolysin are known which may play a part in removing traces of thrombin and fibrin formed "accidentally" in the blood-stream. Circulating heparin is not known to be present except in anaphylactoid states and shock; this substance is formed by the tissue mast cells and may be available locally to counteract clotting in the smallest vessels. The inverse relation between this substance and lipids is interesting; heparin has a clearing effect on the fat chylomicrons after a fatty meal, and lipoproteins are thromboplastic.

Thrombin is not used up in the formation of fibrin from fibrinogen, and is effective in very low concentration; most of it appears to be adsorbed by the fibrin, but once the blood flow past the area has stopped clotting will stop as soon as there is no fresh fibrinogen. As long as there is fluid blood in relation to the thrombus, there is a tendency for fresh "propagated thrombus" to be added, but since

this does not normally proceed indefinitely, the mechanism of clotting must become saturated at some point, though there is little evidence where.

When these mechanisms are defective, the pathological process of *thrombosis* or intra-vascular clotting is found.

The causes of local obstruction to the blood transport are described below.

Obstruction in the Lumen

Four substances are found obstructing the flow of fluid blood. Far the most important is blood clot (thrombus); rarer are cellular masses derived from malignant tumours; and, accidentally, air and fat globules may be found in the vessels.

The formation of clot in the vessels during life is known as *thrombosis*. This may occur in any vessel, heart, artery or vein. The thrombus may remain in the place where it is formed, or it may move in the circulation as an *embolus* travelling with the blood as far as the lumen of the vessel will permit and then becoming impacted —*embolism*. Thrombotic emboli may be of any size and obstruct any vessel from a capillary to the aorta or pulmonary artery. Since veins become wider along the flow, clots will not be held up in them unless the flow is reversed because of some obstruction (retrograde venous embolism) or in the portal circulation where the vein breaks up in the liver into smaller branches; but thrombi becoming loose in the heart or arteries will inevitably end up as emboli in the pulmonary or systemic circulation depending on their site of formation. Exceedingly rarely a thrombus may pass from the systemic veins through a congenital patency in the cardiac septa into the systemic arteries (paradoxical or crossed embolism).

THROMBOSIS. This is not simply a precipitation of fibrin; it represents the organized building up, layer by layer in the stream of flowing blood, of a mass of platelets and fibrin in a fine meshwork with red cells entangled in its interstices. This is normally attached to the vessel wall at its point of origin, though only lightly at first.

The causes of clotting in the blood-vessels during life may be considered under three heads, though as always in pathology, it is common to find more than one concerned. These are (*a*) alteration to the vessel wall, (*b*) stagnation in the flow, (*c*) increased viscosity of the blood, or alteration in the clotting mechanism.

(*a*) Alteration to the vessel wall may be inflammatory—the veins draining an area of purulent inflammation, an aorta with syphilitic aortitis; degenerative changes in the vessel wall, which are mentioned below (p. 132); the invasion of the wall by malignant growth;

even the death of the wall may be responsible in cardiac infarctions for the formation of mural thrombus on the inner surface of the dead muscle—aided by relative immobility of the blood next to this area.

(*b*) Stagnation in the flow—the best example of this is the thrombus that forms in the auricular appendages when the auricular muscle is fibrillating, e.g. in rheumatic heart disease or hypertensive heart failure. The clot that forms in the sac of a syphilitic aneurysm is partly due to stagnation but partly to the damaged wall; similarly that in a surgically ligatured vessel is partly formed over the ligatured part. A special case of some importance is the clot that forms in the length of vessel rendered stagnant by some other thrombus—this extension of clot is known as propagated thrombus and since it may occupy a length of vessel with only a small anchorage to the wall, and possibly an indirect one at that, propagated thrombus is particularly prone to become detached and float off as an embolus.

(*c*) Alteration in the contents of the blood—abnormalities in the clotting mechanism (p. 126) are usually in the direction of less efficient rather than more efficient clotting. The conditions most clearly related to the formation of thrombus in the blood are those in which it becomes viscous either from severe dehydration (prolonged wasting diseases especially with vomiting, such as infantile diarrhoea) or from an increase in the mass of circulating cells and platelets in the blood. The platelets are increased both in numbers and in viscosity for a period beginning about 48 hr after such trauma as a surgical operation. Platelets are increased in erythraemia together with the great increase in the red cells; in chronic myeloid leukaemia there may be 400,000 large white cells in 1 mm^3. Spontaneous clotting is observed in these conditions.

POST-MORTEM CLOTTING OF BLOOD. It is a matter of importance and sometimes of difficulty to decide at autopsy whether a mass of clot is ante mortem and therefore may have had some bearing on the death, or occurred post mortem. When the heart action stops, the blood settles, and the red cells form *rouleaux* and drop to the bottom, until clotting occurs. The normal mechanism of clotting takes place during the first hour or two after death, but in those previously healthy a fibrinolysin acts on the fibrin as it forms, so that a few hours later the blood-vessels contain blood which is fluid, and since the fibrinogen has been used up, will not clot. In persons dead from cachexia or infections, who make up the greater part of those seen in hospital post-mortem rooms, there is no fibrinolysin, and these are therefore found to have clotted blood in their vessels, which will be partly or wholly separated into cells and serum

clot, therefore, which is clearly separated into cells and serum cannot have formed in living blood. Further, the smooth-surfaced fibrin clot formed after death is coarse-fibred and weak, and the clot therefore unravels in water. On the other hand, if a clot shows any sign of organization, such as adherence to the vessel wall, or if the organ shows any effect of the presence of the clot, or if the form of the clot shows it could not have formed in the vessels where it is found, but has moved as an embolus, it is quite certainly an ante-mortem thrombus, and may have killed the patient. More detailed examination will show that ante-mortem thrombi are friable, have a finely granular surface and are often laminated on section, showing that they have been formed in moving blood. The same principles underly the histological distinction in sections between these two forms of clot.

The rarer forms of emboli in the lumen of the blood-vessels are—

TUMOUR EMBOLI. The spread of malignant tumours (p. 214) is in part the result of the invasion of venules by clumps of tumour cells. These, often covered with thrombus, become dislodged and end up where the vein once again breaks up into capillaries: portal or pulmonary capillaries. The tumour cells are not merely a mechanical block, but a living cellular one, and can grow through the capillaries and so spread further, by the arterial tree, where they may reach any part of the body. In general these emboli are rather below naked-eye vision, but gross ones can be seen from time to time.

FAT EMBOLI are a consequence of trauma of any adipose tissue, but particularly the bone marrow in multiple fractures. As a minor event they are very common, but occasionally they are so numerous that they obstruct the pulmonary circulation, leading to dyspnoea, frothy sputum, pulmonary oedema and death; they may pass the lungs and bring about coma by impacting in the cerebral capillaries.

AIR EMBOLISM is a consequence of massive introduction of air into veins. There are three common causes: (*a*) intravenous infusions given under pressure, when the volume of fluid in the giving bottle is allowed to fall below the exit tube, so that air under pressure is carried in; (*b*) syringing the vagina in pregnancy, usually but not necessarily in an attempt to procure an abortion—the air is forced under the placenta and into the widely dilated uterine veins; (*c*) it is a possible complication of surgical operations on the neck and chest, including induction of a pneumothorax or pneumoperitoneum. If the quantity of air is trivial nothing happens; the block is local, and the air ultimately absorbed. If the amount is great, it causes

so much frothing in the heart that the circulation stops and sudden death takes place, characteristically after an interval of ½-3 min. from the introduction of the air.

An allied condition occurs when men who have been working under compressed air are too rapidly decompressed. The gases in physical solution in their blood boil off, and the bubbles throughout the body cause great pain, particularly in the muscles; necrosis of parts of joint surfaces and death have occurred.

Obstruction in the Wall; the Arterial Degenerations

This is at the present moment a most important problem in human disease; death from coronary artery disease is common enough, ill-health from arterial disease in the brain an almost greater social problem in the aged.

The terminology is somewhat uncertain; the expression " arteriosclerosis " is best regarded as a clinical description of an artery, which may have gained this " hardness " from several causes, of which *muscular hypertrophy* associated with hypertension is the principal; calcification of the medial coat (*Mönckeberg's sclerosis*) affecting the media of the lower limb vessels also results in hardening of the vessels; but the most important is *atheroma* which is a change in the intima that is only secondarily and irregularly calcified, and does not at first harden the artery at all. The term " atherosclerosis " is therefore no improvement on " arteriosclerosis," and the additional " arteriolosclerosis " sometimes used to describe degenerative lesions in the smallest arteries is both cumbersome and insufficient, since there are two conditions included. Therefore, while appreciating that clinically it may be useful to have a general term to cover arterial degenerations which cannot be clinically separated, definite terms each meaning one thing are better pathologically, though they are often combined in their effects on any given artery. These heads will therefore be taken—

1. Atheroma.
2. Medial degenerations: (*a*) Mönckeberg; (*b*) Mucoid degeneration.

The arterial changes of hypertension—

3. Diffuse hypertrophy of media.
4. Endarteritis fibrosa (Benign Hypertension).
5. Fibrinoid arteriolar necrosis (Malignant Hypertension).

and

6. Inflammatory arterial disease: Bürger's disease (Thromboangiitis obliterans) and Giant-celled arteritis.

1. ATHEROMA. This common change is seen in the post-mortem examination as scattered plaques of soft yellow material in the intima of arteries of all sizes; the name is derived from the appearance of this material (Greek, *athere*, porridge). In the bodies of young adults it will be seen as isolated points and streaks at well-defined places in the arteries commonly examined at necropsy (these are fewer than they should be; little knowledge is available about the condition of limb vessels, though we have many records of the coronary, cerebral and trunk arteries). As the condition advances, the plaques enlarge to up to an inch across, and in the lower abdominal aorta may form a confluent plaque for its whole length. Two secondary changes become conspicuous: the association with thrombus on the surface and calcification in the deeper part. On histological section, the plaques show a mixture of fibrous tissue on the surface with amorphous fatty mush, sometimes with cholesteride crystals and calcification, deeper in; part of this fatty material is often in foam cells. The wall deep to the plaque is thinner than the rest. The appearance of bulging into the lumen is not seen if the arteries are fixed at the arterial pressure before being opened; the deposit pushes into the wall rather, but a large plaque always deforms the wall. The disease may be quite sharply limited to one part of the circumference of the artery—the signet-ring type of plaque. Thrombus of varying ages is commonly added, sometimes in a series of ages suggesting several sharply separated attacks of thrombosis rather than a continuous slow deposition; this may be seen to be undergoing organization like thrombus elsewhere (p. 145).

Although the plaques reach their largest and most impressive in the aorta, they are really more important in smaller vessels where the lumen can be less easily spared, and as a source of disease the blockage of medium and small arteries is the most important. When any part of the system is partly protected from the pressure of the blood, there is less atheroma in it, e.g. beyond a block by atheroma or beyond co-arctation of the aorta.

It will be seen there are two points to be considered in its aetiology: what the material is derived from, and why it is deposited in the places where it is always found, and not elsewhere; it has not either the diffuse coating or the completely random punctate distribution that would be expected if it was merely the deposition of some blood-borne material. That the basic material is fatty when it is found is clear, but this does not mean that it is necessarily derived from the blood fat directly.

Aetiology of Atheroma. (*a*) Relation to fat in the diet: statistical observation of the incidence of atheroma and its results has shown

that where animal fat is poor in the diet: in the Japanese, whose diet does not include much fat, and who have reliable mortality statistics; in the population of Scandinavia during the war when they no longer had uninterrupted dairy supplies; in the less well-to-do social classes in Britain and U.S.A.; and in the Bantu tribes of South Africa, compared with the white population, there is little or no atheroma. The case of the Bantu is complicated by other deficiencies in their diet and possibly in the age at death; and mortality statistics are slightly upset by the fact that death is usually due not to atheroma alone but to thrombosis overlying it; these things may therefore be related to the thrombosis and not to the atheroma.

(*b*) Relation to the serum lipids: it has been known for some time that in conditions where the blood cholesterol is raised, there is excess of atheroma: diabetics, chronic nephritics, and myxoedematous patients for example. More recent studies have suggested that the protein-bound lipid known as the beta-lipoprotein is the more important fraction of the blood to be raised. Dietetic measures aimed at reduction of blood lipid levels, either by vegetarian diets (for plant fats unlike animal fats do not raise the blood lipid level) or by reducing diets with low calorie intake, are therefore fashionable.

(*c*) Relation to age and hypertension: the incidence of the disease is capricious; the age of the patient does not accurately point the amount of atheroma, though only traces of it are found before the age of thirty, except in sufferers from nephritis or diabetes. It increases thereafter to become very common in middle life, but those who reach an advanced age do not show an excess; often the reverse—that is one reason why they have lived so long. Age will not explain why the sites of the plaques are so local and so constant.

It is usual for a patient who has hypertension to show much atheroma; the relation is clearest in pulmonary atheroma, which does not occur except with raised pulmonary artery pressures from mitral stenosis or emphysema. But the plaques are too scattered and small to provide the block necessary to cause hypertension directly, though a small local patch in the renal artery may do so indirectly, acting by the release of pressor substances from an ischaemic kidney; indeed in a fair number of patients severe atheroma is found with no hypertension—described as " decrescent arteriosclerosis " by Allbutt.

Endocrine factors are likely to be involved; oestrogens lower cholesterol levels in the blood, and women are known to tolerate arteriosclerosis better than men.

(*d*) Experimental feeding of rabbits with cholesterol resulted in

atheroma, but this is somewhat unnatural, as the doses were large and herbivorous animals do not normally receive much cholesterol; the experiments have been repeated on dogs, however, and appear significant.

(*e*) The derivation of the whole affair from thrombosis has been suggested recently by Duguid; fibrin thrombi can be shown on the intima in small quantity, and the histological stages of transformation of thromboses into atheromatous plaques have been described. There is no doubt that fibrin can be a source of fatty material, but there is some doubt whether there is enough of it, and whether the absence of iron derived from red cells incorporated in the thrombi can be explained. There is no doubt that the material comes from the blood-stream; the form in which it exists in the made plaque is not necessarily that from which it starts; but this theory does not touch on the localization of the deposits nor does it explain the associations given above with blood lipids. The localization may be the consequence of strains in the wall leading to small patches of weakness which are sealed by fibrin, which would fit with the constant form and distribution of the plaques in relation to mechanical strains on anatomical forms of artery; the association with fat may be due to the thrombosis and not to the atheroma. Florey has recently demonstrated experimentally the uptake of lipid from the blood by endothelial cells.

Consequences of Atheroma. (*a*) Thrombosis: whether this is really a part of atheroma or a consequence of it, thrombosis is the most important factor in completing the blockage of the artery; without it, there is nearly always a trace of lumen left by the atheroma.

(*b*) Weakening of the wall occurs below it, as shown by thinning of the muscle and fibrosis; this may be due to diminished access of nutrients from the lumen to the muscle. Although it leads to tortuosity and sometimes to shallow outpouching of the wall, the formation of a real aneurysm from atheroma is uncommon.

(*c*) Embolism into the arterial tree from the plaque may occur, but the shower of small lipid fragments is not followed by gross blockage; this is always a consequence of the dislodgement of thrombus from the surface of the atheromatous plaque.

(*d*) Haemorrhage into the plaque is described, particularly in cases of sudden death. The reason for such haemorrhages is not known, and many patches of atheroma are not vascular; when the patch is new it is more usual for the blood to represent fresh thrombus.

2. MEDIAL DEGENERATIONS. Mönckeberg's calcification of the media is a common finding in the leg arteries of elderly men, less common in other arteries. The calcium is deposited deep in the

muscular coat, in fine granules which aggregate into transverse bars demonstrable by X-rays or palpable at autopsy (goose-trachea arteries). This calcification (which may be replaced by bone) is a much less important calcification than that of atheroma; the medial disease need not be attended by any symptoms, though the inability to dilate may lead to pain in the muscles of the leg on walking fast (" intermittent claudication "); when there are signs of block, the cause is usually atheroma inside the medial coat, often in the leg arteries forming as a diffuse fibrous and calcified coating, rather than isolated plaques.

Mucoid degeneration, also known as medio-necrosis, is again a disease of elderly people, in which the intermuscular substance of the arterial media is replaced by a quantity of material with the staining reactions of mucin. Often no ill results from this, but this degeneration in the aorta is always present when there are *dissecting aneurysms*. The name implies a split of the media, and blood from the lumen under pressure finds its way into the medial coat and splits it for some distance. This is a painful process; the patients are suddenly very ill, and the extreme pain suggests coronary heart disease or perforation of a peptic ulcer. In the process of splitting, the branches of the aorta may be occluded by the blood, and so help the diagnosis; the blood may find its way back into the lower aorta or rupture fatally into the pericardium or pleura or mediastinum. A curious result of the fixity and disturbance of the aortic wall is the formation by the heart's action of a transverse rupture through the ascending aorta just above the valves, with fatal haemorrhage into the pericardium.

The arterial changes seen in hypertension are described in the following sections.

3. DIFFUSE HYPERPLASTIC SCLEROSIS. Under this rather cumbersome term comes the medial muscular hypertrophy in small and medium arteries that is the obstruction which the heart has to overcome by increasing the pressure and which maintains the pressure. The reasons for this muscular action are obscure, but many of the drugs used in the treatment of hypertension act by paralysing the sympathetic nerve impulses which help to maintain the spasm. It is the diffuseness and uniformity of this process that make it so important and atheroma so unimportant in causing hypertension. Atheromatous deposits of course would not be affected by anti-sympathetic drugs. Unfortunately the muscular spasm is followed by fibrous replacement of some of the muscle, and again the drugs

can be less effective. The complications of added atheroma and Mönckeberg's degeneration are usual.

4. ENDARTERITIS FIBROSA. In the arterioles, microscopic changes in the intima add to the medial changes described above. The intimal cells are increased and not only is more fibrous tissue present, but also the internal elastic lamina is reduplicated, so that the term " intimal elastosis " is used. Accumulation of granules of lipid, comparable to atheroma in larger vessels, are added, and finally the whole vessel may be closed by a combination of hyaline fibrosis and fatty change described as " fatty-hyaline " degeneration.

5. FIBRINOID NECROSIS. While the preceding changes may be seen in any case of hypertension, and even in old people without significant hypertension, this change is found in addition to the above in *malignant hypertension*, and in the allied conditions of type I nephritis and polyarteritis nodosa; in both of these an allergic basis is likely. In malignant hypertension on analogies from animal experiments, it may be related to the speed and severity of the rise of pressure, and be purely mechanical and not chemical, though this is not proved. The result is the infiltration of the entire vessel wall and lumen with material staining like fibrin, which may in fact be fibrin derived from the blood in the lumen; haemorrhage and inflammation around occur variably, more inflammation in polyarteritis and more haemorrhage in malignant hypertension. The lesion may heal by fibrosis, and possibly recanalize (Plate 12).

6. INFLAMMATORY ARTERIAL DISEASE. Except from syphilis (p. 78) arteries are protected by their thick wall and the direction of the flow of the blood away from them against most inflammations, in contrast to the veins. Infected emboli lodging in them set up a purulent inflammation in the wall with destruction and stretching of the wall, known by the old term of " mycotic " aneurysm. Inflammation that is either chronic or severe will in time penetrate the wall, but the thick muscle slows this up long enough for endarteritis and thrombosis as a rule to close the lumen and minimize the danger; ulceration of a pulmonary artery in pulmonary tuberculosis is a cause of haemoptysis and that of a gastric artery leads to haematemesis or melaena in gastric and duodenal ulceration.

Two special inflammations particular to arteries are of more consequence in causing blockage—

Thrombo-angiitis obliterans (Bürger's disease) is the more important, an inflammation of the smaller distal limb vessels, both arteries and veins, occurring in young men; the first inflammatory changes are less seen and less known than the later obliterative, very poorly recanalized old thrombi. Symptoms of insufficient blood supply to

muscles come on early, relief from anti-spasm measures is temporary, and gangrene of the limb is usually anticipated by amputation.

Giant-cell or temporal arteritis in older people has a similar inflammatory and obstructive course, but affects small arteries (though it may be more widespread) usually in the skull, as the name suggests; the retinal artery may be affected. The other name alludes to the histological picture of the acute stage, with giant-cells around fragmented internal elastic lamina.

Nothing is known about the causes of these two diseases.

The Veins

The thinness of the walls and the drainage of blood into them makes them liable to thrombosis and inflammation from neighbouring sources, but little work has been done on changes in their walls. Even the common and disabling *varicose veins* of the lower limb have no clear and agreed causation. The valves are incompetent, notably those in the long saphenous, and on the veins communicating between the long and short saphenous and the inner veins of the calf, but what destroys the valves is not known; possibly thrombosis over them, possibly stretching of the wall which supports them; as the valves do not increase in size they are bound to become incompetent in any dilated vein. When the communicating veins are incompetent the blood is forced by action of the muscles of the calf out of the deep veins into those of the subcutis whose valves are ineffective and which have no adequate muscular power to return this blood so that it stagnates in the lower limb. Secondary changes of inflammation in the vein wall contribute to the insufficiency of the return of blood, and the end is a group of dilated tortuous channels with more or less fibrous walls partly irregularly blocked by thrombosis.

Aneurysms

A note on these, which may result from several causes, is not out of place. The term literally means a stretching of the wall, the force for which is usually the heart's action and the blood pressure, and this is never sufficient to stretch healthy muscular walls. An aneurysm, therefore, implies damage to the muscle, and this may be—

1. CONGENITAL—malformation of the wall. This has for some time been considered to underlie the " berry " aneurysms of the intra-cranial arteries, rupture of which causes subarachnoid haemorrhage. Certainly malformations of arteries are common at all sizes of artery.

2. TRAUMA. Complete rupture of an artery usually results in retraction of the cut ends and sealing by thrombosis. Incomplete wounds from knives or firearms may result in the wound gaping because of the elastic and muscular coat, and the blood poured out is walled off by fibrosis. This swelling is known as a *false aneurysm* (not composed of the whole artery wall); it may communicate directly or indirectly with a vein near the artery which has been injured at the same time (arterio-venous aneurysm, aneurysmal varix); this sort of communication may also result from congenital malformation, and a curious consequence is that the vessel proximal, as well as the vein receiving the high pressure blood, may become tortuous and dilated. Big leaks of this sort from the arterial tree have noteworthy cardio-vascular consequences (p. 151).

3. INFLAMMATION. Syphilitic and mycotic aneurysms have been already alluded to (pp. 79 and 137).

4. DEGENERATIVE CONDITIONS leading to aneurysm are mucoid degeneration and to a slight extent atheroma (p. 136); but extensive atheroma in an aneurysm is not evidence of atheroma as a cause, since the media weakened by any cause, syphilis for example, is always plastered over with atheroma.

When cardiac muscle is replaced by fibrous tissue, in the healing of an infarct, this in turn may be stretched by the heart beat; the result is a cardiac aneurysm.

The intermittent pressure caused by a pulsating aneurysm is one of the things which can stir up bone erosion; indeed the pulsating enlarged intercostal arteries acting as bypass for coarctation of the aorta can also do so, as may be seen by radiography of the ribs; aneurysms, therefore, erode bone, and may cause pain and produce unusual lumps by so doing.

Infarction

When blockage of a blood-vessel is complete, the part it supplies will die from oxygen lack, unless there are other channels of supply. This is equally true of arterial blockage, where the part receives no blood, and of venous blockage, where the part is indeed distended with blood, but the blood is not oxygenated. To these processes the term *infarction* is applied, and the necrotic area is known as an *infarct*: like dead tissue anywhere, the infarct excites an inflammatory response ending in its removal, if the patient survives long enough.

The cause of the vascular occlusion may be any of those mentioned in the last chapter: embolism, thrombosis, pressure on

blood-vessels from outside. Two main kinds of infarct are recognized, *arterial* (also known as anaemic or pale) infarcts following arterial blockage, and *venous*, which are always purple from the pouring in by the arteries of blood which cannot be removed by blocked veins; this "stuffing" with blood is the literal meaning of "infarct." Both types may be *aseptic* or may become infected either because the thrombus causing it was infected (pyaemic infarcts) or by spread of adjacent bacteria into the dead tissue; this is an excellent culture medium if moist, and the cause of the infarction makes it impossible for a normal inflammatory reaction to occur in it.

ARTERIAL INFARCTS. The presence or absence of an adequate collateral circulation will determine whether an arterial block will or will not be followed by infarction. The artery concerned may be anatomically an *end artery* (central artery of the retina, afferent artery of a glomerulus) but it is better to consider as an end artery all arteries which have no adequate collateral circulation, rather than those which strictly have none at all. An artery which in health has an adequate collateral circulation may lose this because of atheroma or other *block in the alternative vessels*—a good example being the limb arteries of elderly people; there is in health an adequate collateral circulation round the knee, but in elderly people a block in the popliteal space may lead to gangrene of the foot. Further, the collateral circulation may not have time to dilate before the part dies; the *rapid block* of embolism is therefore more likely to be followed by infarction than the slowly building up thrombus. The length of vessel affected is also important, for as well as blocking the main artery, the clot may occlude the origin of the branches forming the collateral; the favoured point of lodgement of emboli, overriding the fork of such arteries as the aorta or the brachial, helps in this. It is only when these points are taken into account that the result of blockage of any given artery can be predicted.

Time comes into the picture in other ways. First, there is a very great variation in the time that different tissues can endure anoxia. In general the more specialized and active a tissue, the shorter the time; thus the cerebral cortex will show infarction if a collateral circulation does not take over or the block be cleared in under a minute.

Secondly, from the pathologist's point of view, time will be necessary to show the visible changes of infarction. The heart of a patient who drops dead instantly from coronary blockage will show no visible signs of infarction; the longer he survives the more obvious the changes will be.

The shape of the infarct is in general pyramidal, with the blocked artery at or a little outside the apex. This is a consequence of the distribution of the artery and the available collateral circulation. In general, an infarct is smaller than the position of the block would lead you to expect: a popliteal block may show a patch of gangrene limited to the foot. Put another way, the block in the artery is always outside the infarct and you must look for it further outside the dead tissue than you might.

Typical arterial infarcts are seen in the spleen and the kidney (Plate 6) with sharply cut outlines, wedge-shaped in sections, and borders much straighter and more clear-cut than inflammatory processes, which tend to be ill-defined and rounded. (Straight lines and sudden onsets in the whole of pathology mean something mechanical, in this case the blockage of the artery.) In the very earliest stages, the infarcted area is slightly swollen and purplish, from reflux of venous blood into the tissue, and the breakdown of its components into substances of lower molecular weight and therefore higher osmotic pressure, which increases the amount of water in the area. This stage is followed by increasing pallor and shrinkage as the blood and products of haemolysis diffuse out. The form of necrosis seen is that known as coagulative—the outlines of the cells are preserved though the nuclei are lost (Plate 6). The border of the infarct becomes engorged from the inflammatory reaction (a straightforward acute inflammation with a moderate number of polymorphonuclear leucocytes) which begins all round the periphery, removes the dead tissue, and ends by leaving an inconspicuous fibrous scar at the site of the infarct some months later. Where a serous surface is exposed, a fibrinous exudate forms over it as over other inflammatory foci. In the course of removal of the blood in a vascular organ such as the spleen or lung, blood pigments (both iron and haematoidin) may be formed in quantity in the area.

CARDIAC INFARCTION. This important clinical condition may be used to illustrate the subject in detail. The coronary arteries are normally distributed: (*a*) the anterior descending branch of the left to the front of the interventricular septum, the apex and anterior wall of the left ventricle; (*b*) the right coronary and the circumflex branch of the left form a ring around the base of the heart which supplies the back of the heart and the left side of the left ventricle, the two vessels varying a good deal in their size reciprocally. There are therefore two main kinds of cardiac infarct, the anterior and apical group related to occlusion of the anterior descending coronary, and a posterior group in which the other arteries are involved. Because of the pattern of distribution of the branches of these

arteries, the shape of cardiac infarcts is usually an irregular plaque affecting the inner two-thirds of the wall more than the outer part. The quantity of myoglobin broken down in the dead muscle alters the normal pale stage of an arterial infarct to a bright yellow stage.

Later Clinical Stages in Cardiac Infarction. The patient may die immediately of ventricular arrest but if the myocardium rallies after the moment of occlusion and the process of infarction begins, the next moment of particular danger is about the fourth day when the inflammatory process of digestion and removal of the dead tissue is going on and before there is much fibrous tissue to support the gap. The peril here is *rupture of the heart*, the healthy surviving myocardium thrusting the blood through the digested area, with haemopericardium, tamponade and immediate death. This is apt to occur in patients with a relatively slight infarct who remain ambulant, and therefore may be a cause of sudden death in the street. Rupture of the heart is practically confined to this condition, the early stage of cardiac infarcts referred to as myomalacia cordis.

After about ten days, this danger recedes from the formation of fibrous tissue; this may be stretched while young into a bulge up to two inches across ("cardiac aneurysm") which can erode the ribs; but this fibrous tissue is less likely to rupture. A fresh source of death comes in the dislodgement of the *mural thrombus* over the inner surface of the infarct to form emboli in systemic arteries; this in turn is reduced by organization into fibrous tissue which forms the thick white lining often seen in the ventricular surface of an old infarct; earlier, the thrombus reinforces the weak area.

GANGRENE. When infarction occurs in a limb, the clinical term "gangrene" is used. It is seen far most often in the lower limb, because the arterial tree in the lower limb is more affected by degenerations and much more affected by aortic atheroma and its consequences than the arm arteries. In the leg, the arterial supply of the skin and the muscles are dissociated, so that some patients complain of muscular pain on exertion (intermittent claudication) whereas others have little pain, but ulceration of the foot, gangrene of the toes and lividity of the skin of the leg. The pain in ischaemic muscle is characteristic and a very important guide to the state of its blood supply; the vascular supply of the skin is judged by skin temperature tests associated with induced vasodilatation by drugs or by immersion of the arms in hot water. The position of the block is more accurately assessed by angiography than by clinical methods, and its position is of great importance if any surgical measures are to be attempted. It is often multiple and diffuse; major sites specially picked out are the aortic bifurcation, the origin of the profunda

artery, the bifurcation of the popliteal artery, and perhaps most frequently the adductor canal.

Natural separation of the dead tissue is usually anticipated by the surgeon, but in time an inflammatory line of demarcation forms between the healthy tissue and the dead and the latter is sloughed off; separation of the dead bone is always late and unsatisfactory. The dead tissue if kept dry becomes black and mummified; if it is allowed to become moist it is certain to become infected (moist gangrene). The neighbouring tissues just kept alive by the collateral circulation may not be very healthy and in particular may not be able to carry out a vigorous inflammatory response in healing amputation wounds.

CEREBRAL INFARCTS. The shape of these is determined by the distribution of the cerebral arteries; as these arteries have a very good anastomosis, infarcts would be rare if it were not for the very low tolerance of anoxia by nerve tissue. Emboli derived from cardiac vegetations or thrombi are frequently a cause, but atheroma and thrombosis are seen particularly in the basilar region, from which end-arteries penetrate into the basal ganglia and brain stem. The form taken by the necrosis is colliquative, the dead tissue being finally represented by a shrunken thin-walled cyst with brown staining of its wall.

PULMONARY INFARCTS. These are due to the occlusion of branches of the pulmonary artery. Because of the presence of the bronchial arteries, death of the lung substance does not result from blockage of the pulmonary arteries, unless the pulmonary circulation is previously embarrassed, as in mitral stenosis, emphysema, cardiac failure; small emboli from systemic veins are usually absorbed without infarction, but really large emboli and infected emboli are exceptions to this and cause infarcts.

Pulmonary infarcts are always haemorrhagic, because of the spongy texture of the tissue and the abundant blood in the pulmonary veins and the bronchial arteries.

INFECTED ARTERIAL INFARCTS are found in pyaemias—acute and subacute bacterial endocarditis; they may also result from secondary infection of the dead tissue. The inflammatory response is always more severe in such infarcts, and it may be grossly purulent in acute bacterial endocarditis; the size of the focus and the amount of necrosis determines whether the better term is pyaemic abscess or infected infarct. In subacute bacterial endocarditis, the virulence of the organism is so low that pus is not found, though the infarcts contain bacterial colonies. The artery containing the thrombus however may undergo aneurysmal dilatation (" mycotic aneurysm ")

because of the spread of the infection to the muscle coat of its wall.

VENOUS INFARCTS. Although venous thrombosis may cause very great disturbance in the tissue fluids in the limbs, it is less commonly a cause of death of the tissues, even when very extensive; venae comites are multiple where arteries are single; anastomoses between them are free, the capacity of unblocked veins is larger, and the direction of flow increasingly easy as soon as the first vessels dilate up. Venous infarction is therefore seen when there is no collateral circulation at all; it is the characteristic infarction of twisted pedicles and strangulated gut. Pressure from outside will occlude the thin-walled veins before the arteries, so that venous infarcts are always haemorrhagic. The pain or other complications of the event usually demand surgical intervention and the natural course of these infarcts is not often seen. At first, the tissue is swollen, opaque, deep purple; as the inflammatory changes move in and organize the dead tissue this blood is broken down with the usual mixtures of yellow and brown pigment, which is present in greater quantity in the scar stages than in arterial infarcts. Pictures of this sort may be seen in strangulated omental hernia, torsion of the testis or of the pedicle of an ovarian cyst, and in tumours which habitually grow into their own veins like the Grawitz carcinoma of the kidney (p. 233).

GUT INFARCTS may be arterial, but the good collateral circulation makes this less common than venous infarcts from mechanical compression of their vessels. Although usually therefore haemorrhagic, in both the rare pale infarcts and the common venous ones, three things are invariable: the muscle coat is paralysed so that obstruction of intestinal movement is present, even when the gut lumen is not itself mechanically blocked; the wall sloughs and permits the emigration of bacteria first, and of gross intestinal contents later, into the peritoneal cavity; bacteria are present in numbers sufficient to make it a septic infarct. They are therefore fatal as a result of general peritonitis in the absence of treatment, which must be rapid. Although often clinically referred to as "acute intestinal obstruction" these are more than the mere blockage of intestinal transport.

HEPATIC INFARCTS. Three kinds are known: (*a*) Blockage of the hepatic arteries gives an arterial, pale infarct with an irregular inflammatory outline, within which all elements of the liver are dead; it is an uncommon event, seen in polyarteritis nodosa or in surgical accidents, and rarely in pyaemia. (*b*) Blockage of the portal venules leads to a slow atrophy of the central parts of the lobules "atrophic infarcts of Zahn" with shrinkage and purple congestion

of the part of the liver. (*c*) Blockage of hepatic venules leads to a condition resembling the nutmeg liver of cardiac failure, " Chiari's syndrome," in the area drained.

Restoration of the Lumen

1. NATURAL. The process of organization of thrombosed arteries or veins is a slow and incomplete one. It will result at best in a capacity of about half the normal and will take several weeks to do so, and therefore cannot be expected to make any difference to the process of infarction: in even the least sensitive tissue, death will occur long before the thrombus is cleared.

The mechanism is an inflammatory invasion of the thrombus by endothelial cells and capillaries, derived from the vessel walls and from the intima throughout the block. Retracting fibrin clot leaves a network of channels in which the longitudinal members dilate up, while between them the process of fibrosis goes on in the clot, with haemolysis and removal of the blood. There is some animal experimental evidence to suggest that this process is expedited by the use of anti-coagulants, but there is no human evidence yet. Restoration of the lumen will clearly make a great deal of difference to the tissues on the margin of the infarct, which have just had enough blood to survive, and will also improve the organization of the infarct itself.

Once the channel is restored, the wall of the new vessel develops the structure appropriate to the original vessel; thus arteries form muscle coats compact with an internal elastic lamina.

2. MEDICAL. It is essential that this should anticipate necrosis; once the tissue is dead, it will have to be removed, by the body itself or by the surgeon. Five methods are available—

(*a*) Dilatation of the vessel and its collaterals by removal of sympathetic tone in the muscle wall—sympathectomy, or the use of ganglion-blocking drugs.

(*b*) Removal of a blocking embolus—embolectomy. When a patient with a known source of emboli undergoes sudden occlusion of an artery, particularly a young patient with healthy arteries, the lodgement of an embolus is likely, and its position may be located and the clot surgically removed; the essential thing is to do so speedily.

(*c*) Removal of the mass of atheroma and thrombus over it from a length of artery—disobliterative endarterectomy. At the end of the operation the artery is represented by the outer part of its muscle coat, but a new intima forms on the fibrin within a few weeks, and

although this would appear to be a local treatment for a widespread condition, in chosen cases it can relieve the block enough to preserve the life and function of a limb.

(*d*) Replacement of the vessel by a graft. Preserved healthy arteries have been used and a range of artificial materials is becoming available, which do not become blocked by propagated thrombus.

(*e*) Formation of an artificial by-pass, without excising the original vessel.

Very considerable technical difficulties have to be overcome with these techniques, and the age and wide distribution of damaged arteries in the sufferers make it unlikely that there will be many long survivals. But pending knowledge which will either prevent arterial degenerations or enable medical treatment to clear the blocks away rapidly, they will give several years respite from limb ischaemia. The problem of smaller less accessible arteries, such as the coronary and cerebral arteries, is still to be tackled.

DISTURBANCES IN THE BLOOD FLOW

I. Hypertension

The pressure at which the blood is delivered to the arteries is adjusted by the resistance offered by the arterial tree (more especially its smaller branches) so that on the one hand the capacity of this tree is not too large for the available blood to fill, as may happen with general vasodilatation and a low blood-pressure, and on the other an adequate volume is delivered to maintain the oxygenation of active tissues. Physiological mechanisms increase the output of the heart in conditions of anoxia, and if this is not balanced by dilatation of the arteries there will be hypertension. Conversely, anything that narrows the arteries, whether temporary muscular narrowing or structural organic block, will require a higher pressure of blood from the heart to deliver the same volume of blood; the physical law (Poiseuille) relating to this shows that the radius of the vessel appears in the fourth power, and therefore even slight narrowing causes a very disproportionate reduction of the volume. The capacity of the heart is limited, by the amount of muscular hypertrophy it can achieve and the pressure which the structure of the arterial wall will withstand, to about double normal pressure, beyond which only a short-lived effort is possible. It will be seen then that in an individual the blood-pressure is adjusted to the quantity of blood he requires and the state of his vessels, and that a man's blood-pressure is not high or low for him, but just right; many people whose blood-pressure is higher than that usually

recorded at their age none the less are healthy and symptom-free. Trouble only begins when the arterial narrowing prevents local oxygenation (ischaemia, infarction) or when the general level has to be so high that the muscle of the heart is inadequate (a failure contributed to by coronary arterial disease) or the small arteries are burst by the pressure (stroke, cerebral haemorrhage). The conditions in which hypertension is found are—

1. PAROXYSMAL HYPERTENSION. Physiological causes—excitement, anoxia, violent action. Increased intra-cranial pressure. Rarely, as the result of noradrenaline secretion by neoplasms of the adrenal medulla (phaeochromocytoma, p. 205).

2. SUSTAINED HYPERTENSION. Narrowing of the vessels relative to the output of the heart, either by spasm of the muscle or structural changes. As a result of this the heart has to push the blood through at a higher pressure.

Pulmonary Hypertension

The raised pressure affects the pulmonary arterial tree.

(*a*) Spasm of the arterioles; in mitral stenosis, possibly a check mechanism to prevent the pulmonary capillary pressure rising so high that pulmonary oedema occurs.

(*b*) Obstruction: (i) Multiple or massive thrombosis or embolism; secondary tumour emboli; endarteritis.

(ii) Emphysema.

(iii) Thoracic deformity.

The exact mechanism causing hypertension in these two conditions is uncertain.

(iv) Congenital heart disease, e.g. patent ductus arteriosus, with shunts from the high-pressure left heart and aorta into the low-pressure right heart; in pulmonary stenosis the right ventricular pressure may be very high, indeed often higher than that in the left ventricle, but that beyond the block in the pulmonary arteries is low.

RESULTS. The right ventricular muscle undergoes very great hypertrophy which enables it for a time to continue the circulation, but in the end the muscle fails. The lung arterioles show atheroma and endarteritis fibrosa.

Systemic Hypertension

This is what is meant by the term hypertension or high blood-pressure, used without qualification.

(*a*) Primary, or Essential hypertension, the common state; at present, cause unknown.

(*b*) Secondary to *renal disease:* a very important group. Damaged kidneys have been shown to discharge pressor substances into the blood-stream and all chronic renal diseases are associated with a rise of blood-pressure in the late stages. It has been suggested that a similar pressor substance is the cause of essential hypertension.

Endocrine disease: adrenal cortical tumours, excess basophil secretion in the pituitary.

(*c*) Co-arctation of the aorta, affecting the arteries proximal to the congenital block near the left subclavian origin.

In the first two groups, the hypertension may show a *benign* or a *malignant* phase, possibly related to the rate and severity of the rise in the blood-pressure. All forms of hypertension are much better tolerated in females than in males, presumably because of the hormonal differences between the sexes.

RESULTS. (*a*) Cardio-vascular hypertrophy. A conspicuous thickening of the left ventricular muscle is paralleled by similar thickening of the arterial media in muscular arteries. In the arteries this is followed by fibrosis of the muscle, so that what started as a spasm and muscular overgrowth (which are reversible) becomes an irremovable stricture. The left ventricular muscle is anoxic, because although the coronary arteries increase in size in these large hearts diffusion from the coronary capillaries into the centre of the thick muscular fibres, obeying the inverse square law, cannot increase proportionately. The muscle though thick is therefore not physiologically healthy.

(*b*) Increased vascular degenerative diseases. Atheroma, which is scattered and mainly affects large and medium-sized arteries, is not sufficiently obstructive to be a direct cause of hypertension, but it is much increased in frequency and severity in the arteries of hypertensive patients, possibly because of the mechanical strain in such arteries. The intimal changes known as endarteritis fibrosa and increase in the intimal elastic layer are diffuse, affect multiple arterioles, and form an obstruction which increases vascular resistance.

Hypertensive patients will therefore suffer from the consequences of vascular occlusion, which is more often the cause of their death than the physical pressure inside the vessels. There are however two direct ill-effects of hypertension—

(i) Vascular rupture—usually affecting the smaller arteries of the basal ganglia, and causing the familiar *stroke*, or cerebral haemorrhage.

(ii) Left ventricular failure—the muscle, possibly weakened by

coronary disease even in the absence of infarction, and locally anoxic, is unable to maintain its output.

Since the renal arteries are among those most commonly involved in atheromatous and endarterial changes, renal infarction (often multiple microscopic infarcts) takes place, and such damaged renal tissue will liberate pressor substances. The process of hypertension thereby becomes self-perpetuating.

REVERSIBILITY. When the hypertension is due to removable causes, such as endocrine tumours or a single damaged kidney, removal of such sources of pressor substances results in the relief of the hypertension and a slow and somewhat incomplete return to normal size in the cardiac and vascular muscle. Fibrotic lesions are not restored. As yet, insufficient time has elapsed since the introduction of such surgical measures to evaluate the long-term effects of a period of hypertension which is brought to an end.

In the absence of removable causes treatment is directed at the suppression of vascular muscular overaction, by surgical excision of sympathetic ganglia or by pharmacological measures blocking these ganglia. Experience of these has shown that mere reduction of the blood-pressure without knowledge of its fundamental cause is of itself beneficial, both by sparing the heart and avoiding vascular degeneration. This is hard to evaluate in the benign phase of hypertension with its slow and unpredictable clinical course, but is abundantly proved by the effects of treating malignant hypertension.

Malignant and Benign Hypertension

Clinical observation on patients separates those with raised blood-pressure (with or without underlying cause) into the larger group with a benign course, who die from the consequences of vascular disease, and a smaller group who die within two years in renal failure. This separation is made largely on the clinical observation of papilloedema, on the fact that the patients look generally ill, and on the signs of renal failure; but pathologically it is clear that there is in this malignant group an additional widespread arteriolar disease which is absent in the benign group, characterized by the presence of *fibrinoid necrosis* of the wall. This change is also seen in allergic angiitis and polyarteritis (periarteritis) nodosa, where it may be related to drug sensitivity, especially sulfa drugs. Although this change in malignant hypertension is seen most easily in the kidney, and proves fatal through failure of the kidney, it is easily found in many other organs, notably the adrenals, brain and gut.

There is still discussion whether this is a separate disease or merely

a more violent phase of the same condition which causes benign hypertension; certainly both in human pathology and in animal experiment it appears to be related to the rate and height of the rise in the blood-pressure. It carries all the dangers of benign hypertension (cardiac failure, vascular rupture, severe atheroma) as well as its own particular dangers of renal failure.

Treatment by removal of a precipitating cause when one is present and by medical measures has shown that the condition is amenable to treatment if not wholly reversible, just like benign hypertension, and because of its bad natural prognosis the improvement is conspicuous.

II. Heart Failure

The heart may be looked on as a pair of pumps linked together, with beds of variable capacity in the lung and the body lying between the output of one and the intake of the other. Like any other pump, the heart has two functions, removal from the venous side and the delivery on the arterial side, and it may fail in either or both these functions; again like any other pump, the reasons for this failure may be classified—

1. Inadequate intake; this clearly does not affect the function of removal.
2. External obstruction to its movements.
3. Blockage of its outflow.
4. Inadequative motive power.
5. Breakdown of its valves.
6. Too high a rate of operation.

The functions of the heart may be divided for convenience into: (*a*) keeping the arterial tree filled with oxygenated blood; (*b*) removing unoxygenated blood from the veins.

The heart may fail clinically in either function and for any of the six reasons, but the results of failure of removal of venous blood are so much more conspicuous pathologically and somewhat more obvious clinically that they are referred to usually as congestive failures. The deficiency in output is minimized by the fact that the patients are observed at rest in bed, when the demands for output are at their lowest; if the patients are observed while active or with exercise it will be clear enough that the function of delivery may be impaired when that of removal is still adequate.

In many or most of the conditions labelled clinically "cardiac failure" the heart is working unusually hard as a compensatory effort, even when it is not itself at fault; it is therefore usually

enlarged from hypertrophy, and it is only when this extra effort is insufficient that actual failure occurs. The causes may be tabulated as follows—

1. Failure to Fill the Arterial Bed with Oxygenated Blood

(*a*) THE HEART IS NOT AT FAULT; it does its best and may considerably increase output. So-called "high output failure" is not really failure of the heart at all—"high output state" is a better term.

Arterial bed too big. The maximum amount of blood the heart can handle even with hypertrophy is limited, and this is particularly true when a sudden increase in volume is demanded before hypertrophy can help.

This occurs in arterio-venus aneurysms, or arterio-venous leaks from any cause—patent ductus arteriosus; in Paget's disease of bone, when the immensely vascular bone has a large capacity for blood; in large or multiple vascular neoplasms; in the vasodilatation of thyrotoxicosis.

Blood too poor in haemoglobin. Severe anaemias.

Lungs will not oxygenate the blood properly. Emphysema. There are other factors concerned as well, e.g. the fatty degeneration of the myocardium in anaemia, the obstruction to output in emphysema.

(*b*) HEART AGAIN NOT AT FAULT; it works to capacity, but cannot increase or even maintain normal output.

Inadequate venous return. "Shock"—severe haemorrhage; peripheral circulatory collapse.

(*c*) LOW OUTPUT HEART FAILURE, with the heart at fault.

External interference. Pericardial effusions, constrictive pericarditis.

The action is partly on the thin-walled veins and atria, partly on the ventricle in diastole: full filling is impossible.

Valve damage. Extreme mitral stenosis, preventing the left ventricle from filling.

This group is also a source of interference with the clearance of venous blood from the veins and so appears also under the head of congestive failures.

Compensation by the rest of the body for a low cardiac output is by intense vasoconstriction in the less important areas: skin, gut, limbs, kidney; it may be so extreme as to cause gangrene of the extremities and cortical necrosis of the kidney.

2. Failure to Clear the Venous Blood

The emphasis is on this function, and so they are referred to as

the congestive failures. But the inadequacy of the output to maintain normal function is clear if the patients are examined otherwise than at complete rest.

Failure of this kind obviously cannot occur if the venous return is low and there is little blood to clear; but the output may be low, normal or even high, because if there is any chance of compensating by hard work or hypertrophy the heart will take it. In mitral stenosis at death the output may be at the resting normal level. The causes are—

External interference (see above).

Blockage to outflow. Arterial hypertension, aortic stenosis: these affect the left ventricle; pulmonary stenosis, pulmonary hypertension, mitral stenosis: affect the right ventricle, and (mitral stenosis) the left atrium.

Inadequate motive power. Genuine myogenic cardiac failure. (*a*) Anoxic: severe anaemias; diffuse myocardial fatty degeneration; large myocardial infarcts. (*b*) Toxic: diphtheritic myocarditis (so-called); potassium poisoning; no available glucose; acute active rheumatic myocarditis; fibrillating muscle.

Certain rare causes: myopathies, Fiedler's myocarditis, Trypanosomiasis (South American type), fibro-elastosis of the myocardium, beri-beri (vitamin B_1 deficiency), primary amylosis.

Damage to valves. Stenosis, notably mitral valve. If the area is reduced from the normal 5 cm^2 there will be dyspnoea, and below 1·5 cm^2 there will be dyspnoea at rest.

Incompetence: an extra volume has to be put out to make up for the reflux, and there is the strain on the muscle in diastole from the other side of the incompetent valve. This may cause great dilatation. e.g. the aneurysmal dilatation of the left atrium in mitral incompetence from the thrust of the left ventricle, and that of the left ventricle in aortic incompetence from rebound from the aortic wall.

Over-fast action: paroxysmal tachycardia; auricular fibrillation.

Insufficient time is allowed for the ventricle to fill properly at rates much over 150/min., and this results in blood accumulating in the venous system, and an insufficient output for the patient's activities except at rest.

Artificial Overfilling of the veins by injudicious transfusions of blood or saline in excess of the capacity of a possibly already weakened heart may cause heart failure.

Consequences of these Defects

In general, statistical equality of the volumes delivered by the right and left sides of the heart must be present, though individual

beats may vary a little. Over short periods however there may be inequalities, and in accordance with the side of the heart more involved failure may be predominantly right- or left-sided. Quite a short time is involved; thus if the left ventricular output is 10 ml below that of the right, it will take little over 1 min. at normal rates to give the extra litre of blood which is found in the lungs in left ventricular failure. Three distinct types of cardiac failure are described—

1. ACUTE HEART FAILURE. Immediate death. This occurs in aortic valve disease, especially stenosis; following rupture of a valve cusp; pulmonary stenosis; large pulmonary emboli; large coronary occlusions. Ventricular fibrillation may occur before the muscle finally stops.

In these acute failures, the distribution of the blood in the tissues of the body will be unaltered. There may be slight accumulation in the right atrium and ventricle, which may be dilated.

2. LEFT HEART FAILURE. Pulmonary congestion, going on to oedema of the lungs—death from drowning and general anoxia. This occurs in any condition associated with obstruction to the output of the left ventricle, and is best seen in heart failure following prolonged hypertension.

At necropsy the pink frothy oedematous lungs will indicate the cause of death, and there will be the associated evidence of hypertension or aortic valve disease.

3. RIGHT HEART FAILURE. Classical congestive heart failure, with congestion of the liver, spleen, lungs and kidneys. This is usually a more prolonged type of failure than the other two, death occurring from medullary and cerebral anoxia due to the venous engorgement, and the changes after death are more complex and obvious. The "cricket-ball" spleen is due to venous engorgement, the reservoir function of the spleen relieving the amount of venous return. The kidneys are firm rather than deeply congested; purple congestion there indicates a more acute type of failure. The changes in the liver are more complex; they are described in the chapter on anoxia (p. 169) and are colloquially referred to as the nutmeg liver. The lungs are rigid from the excess of blood in their vessels and brown from the breakdown of extravasated blood in the alveoli (brown induration). Common causes of this type of failure include rheumatic mitral stenosis and emphysema.

In assessing the cause for failure in an individual patient, it must be remembered that processes will often be mixed, and the failure may not be of a clear-cut type. The diagnosis of cardiac failure,

and of the remote cause, does not complete the picture; always require an immediate precipitating cause. Thus in a patient with a known severe mitral stenosis, it is not sufficient to say that he is in failure because of that valve lesion; it has been unchanged for years, and a sudden change in the patient to cardiac failure will always be due to some new and possibly treatable factor: it may be a recrudescence of the rheumatic infection, thrombotic events in the left atrium, or even an acute respiratory infection.

OBSTRUCTION OF LYMPHATIC DUCTS

These normally return to the blood, by way of the glands and the thoracic duct, the protein part of the fluids in the tissue spaces and a certain proportion of other fluid.

Blockage of the peripheral lymphatic channels is the result of inflammatory fibrosis in and around the glands, usually after streptococcal infection, or the result of filling the glands by secondary neoplasm. The radical operation for carcinoma of the breast provides the commonest clinical example. The result is oedema of the affected limb, the fluid usually rich in protein and the limb indurated. Apart from the discomfort of the swollen limb the condition may cause no trouble for years. Eventually fissuring of the skin and ulceration results.

Blockage of the thoracic duct is the cause of chylous effusions in the peritoneum and pleurae. This is a consequence of the absorption from the gut of all fatty material by the lacteals, which cannot reach the blood-stream if the thoracic duct is blocked by secondary growths. Opalescent effusions are not necessarily of this origin—so-called pseudo-chylous ascites from low-grade inflammation and neoplastic spread in the space is not very rare.

OBSTRUCTION TO THE AIR PASSAGES

COMPLETE OBSTRUCTION, AFFECTING THE TRACHEA OR BOTH BRONCHI. This will clearly result in the loss of air entry and hence *asphyxia*. This can be defined as the condition resulting from obstruction of the main air passages, and so separate from *anoxia* which covers a much wider range of conditions.

A special case of asphyxia arises when the obstruction is due to water (see below, drowning).

The characteristic reactions to obstructive asphyxia are violent efforts to breathe, which result, when the obstruction is in the least incomplete as in most homicidal attempts, in over-distension of the

lung alveoli. Secondly, again with a few exceptions, violent over-action of the heart will occur, until it fails from oxygen lack, and so engorgement and petechial haemorrhages may be seen in areas determined by the position of the obstruction. These haemorrhages are commonly found at autopsy on the smooth intra-thoracic surfaces of heart, pleura, and thymus in infants dead of asphyxia; they are conspicuous in the eyelids and often in the face and brain of strangled people; they are common in patients with long-standing pulmonary emphysema, due to the raised intra-thoracic pressure associated with forcible expiration reflecting on the veins of the head and neck. The degree of congestion and the petechiae may be extreme when the asphyxia is due to gross crushing of the thorax by masonry. After a period of about ten minutes, the heart action ceases from oxygen lack: consciousness may be lost in seconds if the carotids are compressed also, and in any case long before the heart stops.

Where the cause is drowning, in addition to the above a quite new train of events is set up by the involuntary inhalation of water into the lungs, which invariably occurs although a period of breath holding may postpone it. The inhaled water, if fresh, exchanges across the alveolar epithelium with great speed, causing haemodilution and a shift of inorganic ions which is in itself fatal even before oxygen lack. In salt water the shift in the opposite direction is slower and less well-marked. At autopsy the inhaled water is present in the lungs in quantity, and in addition it is possible to demonstrate the electrolyte changes and dilution of the blood if that in the right side of the heart is analysed.

COMPLETE OBSTRUCTION, AFFECTING ONLY A SEGMENT OF THE RESPIRATORY SYSTEM, so that life can be maintained indefinitely.

The air in the isolated segment is absorbed, both oxygen and nitrogen, in a very short time by physical process of solution. Since there is nothing to take its place, the lung collapses, becoming shrunken, dark and airless. The rest of the lung or the other lung over-ventilates to take up the space (compensatory emphysema); if a whole lung is involved the shift of the heart may be demonstrable, and indeed may give rise to clinical symptoms.

Where the collapse is prolonged, some infection is common, but may not occur; the lung then shows interalveolar fibrous tissue, with the alveolar epithelium unusually prominent and cubical, like gland tissue. *Atelectasis* means collapse of lung.

INCOMPLETE OBSTRUCTION. Here there are two sets of events. First the air-entry may be involved in a valvular manner, so that air can get in but not easily out. This is found in bronchial asthma

(p. 91) and sometimes in growths or the inhalation of foreign bodies. The result is *emphysema* or over-distension of the alveoli.

In many elderly people, associated with chronic bronchial infection, a general over-distension of alveoli throughout the lung is found, with consequent dyspnoea. The cause of this is obscure, but deficient pulmonary elastic tissue has been suggested; hence the name *atrophic emphysema* sometimes given to it. It is an important common cause of failure of the right side of the heart.

Secondly, the discharge of the secretions of the bronchi and inflammatory material and inert foreign bodies is impaired. Neither ciliary action nor cough is adequate and stagnation and infection is likely. Hence any persistent obstruction of the bronchus of whatever kind is likely to show itself clinically by infection persisting in and localized to one part of the lung (most spontaneous infections of the bronchi are diffuse and bilateral) and the clinical appearance of local infection should indicate the probability of a local cause. Until this obstruction is cleared it is unlikely that the infection will clear up, and therefore where the obstruction is itself innocent and the part of the lung affected not large the principal clinical danger is development of such a local pneumonia—lung abscess, or (if the inflamed bronchi become dilated) bronchiectasis. The obstruction may itself be serious (e.g. carcinoma of the lung); and the fibrosis resulting from inflammation at the site of a foreign body may keep up the infection after the foreign body has been removed, if it is allowed to remain long enough to cause local ulceration of a bronchus. The development of diffuse dilatation of the bronchus is explained partly on the effect of the infection on the bronchial wall and the muscle in particular, partly on over-inhalation to overcome the obstruction, and partly on the distortion by surrounding peribronchial fibrosis and collapse. When such events make resolution improbable, surgical removal of the inflamed area will avoid the dangers of prolonged pulmonary infection, in particular cerebral metastatic abscesses and amyloidosis.

OBSTRUCTION TO DUCTS

Examples will be seen arising from all three main types of obstruction—pressure from outside the wall, usually by growths of adjacent organs, disease of the wall itself, again notably neoplasms, and stones in the lumen.

The result will be stagnation of the flow; dilatation proximal to the obstruction will develop in time; the organ drained by the duct may continue to secrete, e.g. the kidney where ureteric obstruction is

incomplete may be greatly dilated with urine (hydronephrosis), but if the obstruction is complete the secretory pressure of the cells reacts on their own blood supply and the organ ceases to function. With an incomplete obstruction, infection is the rule, and chronic inflammation and fibrosis will spread through the duct and the gland from which it is derived.

A most important cause of duct obstruction which is not covered elsewhere in this book as the growths are, is the formation of a stone or *calculus*.

Calculi

For the formation of a calculus, three things are necessary—

1. An adequate amount of the material. In biological conditions, this means in the outflow of a functional organ; there is never enough solid in a cyst for a calculus.
2. An organic skeleton to hold the crystals together. Precipitation by itself is not enough; it results in a microcrystalline sludge.
3. Anchorage in the moving fluid in which it grows, to prevent its being washed away while very small.

PRECIPITATION can result from three factors—

(*a*) Excess formation and excretion, e.g. calcium in bone or parathyroid disease, sulphonamide crystals in therapeutics, amino-aciduria in metabolic disease, abnormal formation of oxalates.

(*b*) Dehydration and concentration; urates in infants, sulphonamides in the tropics.

(*c*) Alteration in composition of the solvent—acid urine and urate excretion; splitting of stabilizing colloids by bacteria.

Where the calculus results from the above alone, it is referred to as a metabolic, primary or non-inflammatory calculus. Inflammatory processes contribute to calculus formation: (i) by increasing the viscidity of the fluid by inflammatory exudates, so holding microcrystals together; (ii) by presenting solid particles to act as nuclei for the stone; (iii) by altering the pH, colloids, etc., of the fluid.

Where the inflammation appears to be the primary event, the stones are often called "inflammatory," but the two classes are not entirely separable, since a primary stone formed for one reason may act as a nucleus for the precipitation of an inflammatory coating either mechanically, or by causing ulceration or obstruction in the cavity in which it occurs. For this reason as well as the complexity of the chemical factors concerned, the chemical analysis

of a stone is not necessarily a guide to the cause of its formation and provides only a rough classification of calculi.

None of the foregoing will see a stone large enough to survive in a flowing current and some further factors are required to explain their frequency in the urine and bile.

RENAL CALCULI. The necessary anchorage is found in the lymphatic spaces immediately under the epithelium of the renal pelvis. Randall showed in 1938 the presence of an incrustation on the renal papillae in calculus formation, which formed a basis for the building up of a mass too large to be carried off in the urine. Carr extended this observation in 1943 by showing that lymphatic blockage in this area would result in the accumulation of calcified deposits at this point, and that the masses so formed were physicochemically compatible with the calculi actually found; this also explained why calculus formation might be localized to one part of a kidney.

Causes for the precipitation of material in the pelvis can be found under each of the headings above; thus the renal stones in patients in orthopaedic hospitals can be explained as excess excretion of calcium from a combination of good diet and sunshine with diminished skeletal requirements by patients who are for long in bed; the renal calculi in England in the seventeenth and eighteenth centuries were probably associated with a high-calcium diet (see also p. 177).

The consequences of calculi include: trauma to the mucosa with repeated bleeding, ulceration and secondary infection; this is particularly common with small spiky calculi such as those made up mostly of calcium oxalate. Obstruction to the flow of urine brings renal colic as long as the flow is vigorous; then dilatation of the ureter and pelvis (hydronephrosis) until obstruction is complete, and finally failure of secretion by the kidney. The partially obstructed pelvis is prone to secondary infection (pyonephrosis), which in turn increases the amount of secondary calculus formation as well as reducing the function of the kidney.

Later consequences include metaplasia of the transitional epithelium to squamous keratinized epithelium, and possibly the development of carcinoma; but stones may also form on nuclei from a preceding carcinoma. Stones may move to or grow in the bladder.

There is no natural mechanism for the solution of a calculus or its removal or encapsulation. Surgical removal deals with the consequences, but not with the underlying cause, which may require removal of part of a kidney, or a parathyroid neoplasm. The solution of the stones by irrigating with chelating agents which

withdraw the calcium from the crystals and so disintegrate the stone is a technique that is under investigation.

BILIARY CALCULI. Applying the same principles, the stability of the young calculus is due either to its formation in the intra-mural glands of the wall, or to the formation of the stone on the villi, which may be physiologically heavily loaded with cholesterol. The narrow cystic duct is obstructed by the spiral valve, the opening is at what is for the most of the day the top of the viscus, and even small stones may lodge.

Precipitation may occur from over-production of pigment, in the stones found in spherocytosis and other severe haemolytic anaemias; here the form is microcrystalline and obstructive effects unimportant. The cholesterol in the bile is in any case super-saturated and held in solution by the bile-salts; but over-production may be the reason why cholesterol stones are so much more common in the female (though not necessarily related to child-bearing). Splitting of the bile-salts by bacterial action is the most important contribution of organisms; the bacteria may act as nuclei for deposition, though they can only be small ones, as they have been cultured from the centres of calculi: thirdly the production of excess mucus and inflammatory exudates increases the probability of stones hanging together.

There is little inflammatory about the *pure cholesterol stone*. Light, oval, waxy yellow and radiolucent, with a visible crystalline structure, they float in the bile and leave the gall-bladder wall little inflamed, though they may be associated with much lipoidosis. The common stone in inflammatory conditions is the *mixed stone*, with laminae of cholesterol and pigment and a variable amount of calcium. The more of this, the heavier they are, and also the more visible on radiography; these press heavily on the mucosa, ulcerate it and lead to chronic inflammation and fibrosis, which are self-perpetuating conditions. Replacement of the mucous membrane by stratified squamous metaplasia of the epithelium may occur; carcinoma is rare in comparison with the frequency of gall-stones, but almost unknown without the presence of gall-stones.

Consequences of calculi are (*a*) local in the gall-bladder—chronic inflammation, fibrosis, carcinoma from irritation of the mucosa; mucocele from obstruction of the cystic duct, the mucosa continuing to secrete mucus though hepatic bile cannot enter, but is still free to pass to the duodenum; (*b*) obstruction to the common bile-duct if the stone passes the cystic-duct; this results in biliary colic and the syndrome of obstructive jaundice, with the absence of bile-pigment from the stools and of bile-salts from the fat-absorbing small

intestine; the gall-bladder is usually too rigid from the inflammation associated with the presence of stones to become dilated either with mucus or bile, and so remains impalpable (Courvoisier's law). If the obstruction remains unrelieved, infection of the dilated hepatic bile-passages follows (suppurative cholangiectasis). Rarely the fundus of the gall-bladder becomes attached to the gut (duodenum or transverse colon) and the stone forces its way through the adhesion and cures the condition by ulcerating into the bowel; stones achieving this are usually large and heavy, and so may become impacted in the lower ileum; otherwise they are passed *per anum*.

OTHER CALCULI. Masses of inspissated mucoid secretion impregnated with calcium are found in the duct of the submandibular gland, and more rarely in the pancreatic-duct; the usual consequences follow. Insignificant concretions are found in the acini of the prostate. Concretions of calcified faeces in the appendix are known as faecoliths and may play some part in leading to stagnation and infection of the mucosa of that organ; the term phlebolith is applied to calcified thrombi in the prostatic and retroperitoneal veins which have some radiological importance, in that they may mimic urinary calculi.

OBSTRUCTION OF THE ALIMENTARY TRACT

This is conveniently considered segment by segment.

1. OESOPHAGEAL OBSTRUCTION. The common causes include impacted foreign bodies; pressure from without by aortic, vertebral, or other masses; in the wall, new growths (mainly carcinoma) and a very important group in which the muscles of swallowing are weakened, because of neurological disorders in the medulla (bulbar poliomyelitis, motor neurone disease, disseminated sclerosis), or neuro-muscular disease (myasthenia gravis, cardiospasm).

The obvious consequences of starvation and dehydration brought about by obstruction are often preceded by two less obvious ones. The secretions of the buccal mucous glands are voluminous, and normally are swallowed. Any defect in this mechanism will result very soon in the pooling of saliva at the back of the mouth and throat, and this will overflow into the air passages. The cough mechanism may well be weakened by the same causes that affect swallowing, and bronchogenic infection of the lung will follow. This fatal complication must be avoided by postural methods of keeping the oropharynx dry, particularly in patients in whom swallowing is only temporarily difficult.

The second set of complications follows from the absence of a serous coat, and the absence of room to expand, around the oesophagus. Long-standing innocent obstruction may indeed be associated with quite remarkable dilatation and hypertrophy, but if the wall is damaged by neoplasm, or by the impaction of a foreign body where there is no "give" in the surrounding structures, necrosis and the passage of infection take place into the mediastinum or possibly into the trachea, bronchi, pericardium or pleura. If there were a serous surface, a considerable safety margin would be afforded by the rapidity with which fibrin barriers form on such surfaces; but there is not, and inflammation passes unopposed into the loose areolar tissue around the oesophagus, or into the adjacent structures.

2. GASTRIC OBSTRUCTION. The majority of objects that pass the cardia will pass the normal pylorus; obstruction is therefore almost always due to post-inflammatory scarring following peptic ulceration near the pylorus, or to new growths; in very young infants severe muscular spasm and overgrowth are known (congenital pyloric stenosis); rarely, scarring following ulceration may produce narrowing of the body of the stomach. Emptying by physiological vomiting is the natural sequel; the capacity of the stomach is considerable, however, and there is plenty of room for expansion; in long-standing disease very great dilatation and some hypertrophy are seen. Repeated vomiting will deprive the body not only of food and (more immediately serious) water, but also of appreciable amounts of chloride.

3. OBSTRUCTION OF THE SMALL INTESTINE. Again, the capacity of the lumen is adequate down to the terminal ileum; it is here that foreign bodies becomes impacted. New growths are surprisingly rare, inflammations commoner (again mainly in the terminal ileum); but the small gut with its long free mesentery and great mobility is the part most involved by mechanical interference from fibrous peritoneal bands and hernial orifices. It is most important to distinguish clearly when the obstruction involves the blood supply as well as the lumen; it is less common for the lumen to be involved alone, usually incompletely, as the result of stretching the bowel over some mass, or of stenosis by secondary peritoneal growths. When there is infarction of the gut, the importance and danger of this is such that the obstruction to the transport becomes immaterial. It still provides an important clinical sign, in the violent efforts made by the muscle of the proximal gut to drive the contents on, which cause severe colic; the lethal necrosis of the gut wall is virtually painless.

Most small intestinal obstruction, being due to strangulation, is associated with infarction, and is acute; distension is marked, but there is rarely time for hypertrophy. Emptying of the obstructed bowel by reversed peristalsis and vomiting occurs but is incomplete except when the upper small gut is concerned; distension is then correspondingly less. Chronic obstruction shows the usual dilatation and hypertrophy above the site and collapse below it; ulceration and infection of the wall and the peritoneum may occur, but the relief afforded by distension and the barrier of fibrinous inflammation and, later, fibrosis may localize the damage.

A case of particular importance is the paralytic obstruction that is seen when there is general peritonitis (ileus). This appears to be due to poisoning of the muscle; it results in failure of absorption of normal nutrition and water, and abnormal bacterial flora developing in the dilated and stagnant gut may contribute toxic products; toxaemia and dehydration make this a most serious complication of, for example, neglected appendicitis.

4. COLONIC OBSTRUCTION. Foreign bodies which will pass the ileo-caecal valve will pass the anus, and play no part in colonic obstruction, which is nearly always due to neoplasm of the wall. These are commoner in the left half of the colon, in which the contents are becoming solid; symptoms are therefore often obstructive. As they develop slowly, dilatation and hypertrophy are well-marked, and the activity of the gut may be visible through the abdominal wall. The burden of this excessively vigorous peristalsis is taken largely by the thin-walled caecum; bacterial invasion and ulceration of the caecum is followed by perforation (" stercoral ulcers "), a long way from the obstructing carcinoma, which perforates more rarely.

In the new-born infant congenital malformation of the anus or unusually viscid meconium may cause obstruction and perforation proximally.

INTUSSUSCEPTION is the name given to the travel of any part of the gut into the succeeding segment as the result of peristalsis. The object providing the purchase for this peristalsis is usually a neoplasm, though inflammatory swelling of the terminal ileum may account for an important example in year-old babies. The ileo-caecal region is commonly involved, though any part may be; the lumen is obstructed, but the blood-vessels are soon occluded as the mesentery is dragged in, and venous infarction is the consequence.

DIVERTICULOSIS. The efforts made by the colonic muscle to propel the contents of the left colon may result in forcing bulges of mucosa through gaps between the muscle fibres, often into the appendices

epiploicae. This is seen mostly in elderly obese constipated persons. The pockets of mucosa may be uninfected or may act as a focus for chronic purulent inflammation outside the wall, involving adjacent structures (diverticulitis).

OBSTRUCTION TO THE FLOW OF CEREBRO-SPINAL FLUID

Obstruction to this flow is an exceedingly important factor in the course of inflammation and neoplasia inside the skull. It is discussed with the inflammations on p. 99.

REFERENCES

Coagulation of the Blood

The subject is extensively surveyed in the *Brit. Med. Bull.*, **11** (1955), by a group of the most distinguished workers in the field.

CHAPTER 6

DISEASE DUE TO DEFICIENCIES AND EXCESSES

DEGENERATIVE CHANGES

Two terms are in common use to describe events which have none of the features of an inflammatory reaction, and in which more or less serious loss of effective function is the result. These are " degeneration " and " ageing." Neither of them provides an adequate description, and to state that a change is degenerative explains neither the change that has occurred nor the reasons and steps by which it has occurred. It merely expresses dissatisfaction at the way the tissue has reacted; this contemptuous term should only be used to describe a category of disease in full acceptance of its inadequacy, and as a temporary classification of a pathological change that is neither due to attack from external agents nor neoplastic, and which leads to depression of function.

The reaction is passive, resulting in dysfunction or death of the affected cell; inflammatory responses to this dead tissue are usual, as secondary effects. The mechanisms producing the degeneration are often not known. But these changes are capable of much more precise definition either in chemical or physiological terms, and the aim should always be before us of trying to describe them in such ways.

" Ageing " again is loosely used. It covers two quite different things, (*a*) the mere passage of time, (*b*) the summation of multiple minor injuries, chemical, traumatic, toxic, which occurring from time to time in our lives will contribute each their quota of damage. The number of such injuries an individual suffers will increase with his age, but the injuries are each capable of classification under their proper precise heads, and to do so will point the way to avoiding or curing them.

A pure age change due to mere passage of time must (*a*) affect a tissue uniformly or at least symmetrically; it is no use dismissing a change as merely due to age if it has affected one part of an artery or one joint, and left the other equally old parts or joints unaffected; (*b*) it should be capable of plotting as a straight line or a regular curve against time, so that the patient's age can be accurately told from it. The total quantity of calcium chemically estimated in the

media of arteries shows this, and may be regarded as an age change —an inevitable consequence of spending a given time in this world. Very few of the other conditions sometimes described as age changes will comply with these strict criteria; certainly important degenerations, such as atheroma and osteoarthritis, will not.

The causes of such changes due to age are under investigation. Some may be due to physical changes in the structure of extra-cellular material such as occurs in inanimate metals, e.g. ageing of collagen. In the cells, the enzyme systems may become poisoned, or replacement at cell-division may fail after a number of divisions. When the causes are capable of analysis, they too will probably be classifiable under the heading of poisoning, prolonged stress and similar precise terms. At present we are forced to speak of degenerative disease, but should regard it as a temporary label to be replaced as often as possible by better and more permanent explanations.

The causes of degenerative processes can broadly be grouped under two headings, as far as they are known—

1. Toxic, due to poisonous substances (*a*) of known chemical structure, (*b*) of unknown chemical structure but precise effects, (*c*) due to inferred vague toxic products under investigation. These in turn may each be derived from inside the body (intrinsic) or from the outer world by inhalation or ingestion (extrinsic). If the reaction is sharply necrotizing with an immediate inflammatory response, this is taken to be the major event (e.g. lysol poisoning) and it is classed as inflammation: if the changes in the cells are slow and inflammation is late and an inconspicuous reaction to the dead tissue, the degeneration takes first place (e.g. carbon tetrachloride poisoning).

2. The second big cause of degeneration is *anoxia*. This may arise from many causes: *anaemic*, when there is too little haemoglobin in the blood to carry the oxygen; *ischaemic* when there is too little arterial blood either as a result of stagnation or arterial blockage; *histotoxic* when the anoxia is due to the inability of the cell to utilize oxygen because of poisoning of its enzyme systems. In general, though inadequacy of other nutrients is a possible cause of degenerations, the lack of oxygen is the first one felt; but many degenerative changes are now being shown to be due to long-term shortages of trace materials; some of these are known and described as vitamins; for essential mineral elements the term trace elements is preferred. There are still degenerations which cannot be allotted sharply to any of these categories.

The first cells hit are the active metabolic cells of the body; supporting tissue in general is very resistant to anoxia and toxins, but the central nervous system, the heart muscle, the kidney and

liver all show degenerative changes readily. In the case of the liver and kidney, the part they play in excretion and detoxication make them unduly liable.

It is clear then that of the two main causes of degenerative changes seen in pathology, one is poisoning, the other a deficiency of oxygen. No better example exists of the term " degeneration " as an obscuring bracket over two dissimilar processes, an excess and a lack.

Three levels of intensity of damage to cells by toxic or anoxic states are recognized: *necrosis* where the cell is killed; *atrophy* where it slowly wastes away, without replacement fibrosis; and *degeneration* when cytoplasmic changes are seen. In this usually less severe group there are two stages: *parenchymatous degeneration* (" cloudy swelling " is an older term) and *fatty degeneration.*

NECROSIS is the term employed for local death of the tissue (sometimes " necrobiosis " is used to emphasize that the surrounding tissue is alive). The dead tissue is usually pale, sometimes white or yellow, and characteristically opaque. It may become stained by products of haemolysis. When examined histologically the diagnostic feature is the absence of nuclear staining; the nuclei may be either vacuolated and distended, a process which goes on to the solution of the nuclei in the cytoplasm (karyolysis), or they may be excessively dense and concentrated into small black dots (pyknosis) and fragmented (karyorrhexis); a healthy intermitotic nucleus should show detail in the haematoxyphil nuclear membrane. Changes in the cytoplasm may be seen, but it is a useful convention to regard these as reversible as long as the nucleus is intact; once nuclear degeneration has occurred the cell is dead and cannot recover. The dead tissue is digested and liquefied by its own enzymes (autolysis) as well as by immigrant inflammatory cells.

ATROPHY is the term used to cover shrinkage of cells without inflammatory reaction, necrosis, or fibrosis; it is often used more loosely, especially in *ischaemic atrophy* where there is often small-scale infarction. Good examples are found in wasting diseases (carcinomatosis, starvation, chronic tuberculosis) when the heart and liver of the patients are appreciably shrunken and often dark-brown from the concentration of intra-cellular lipochrome pigments (" brown atrophy "). The lack of nutrition of the cells has an obvious cause here; long-standing vascular narrowing, not severe enough to cause death and infarction, may sometimes produce atrophy. Lack of essential substances in the form of trophic hormones is the cause of *endocrine atrophy*—the thyroid and adrenals in some forms of pituitary disease; physiological examples of this are the atrophy of the uterus and breasts after the menopause, and

that of the thymus at puberty. Muscle fibres show atrophy if disused, and a more extreme atrophy if their nerve supply is cut Disuse atrophy also conspicuously affects the bones and joints of an immobilized limb.

PARENCHYMATOUS DEGENERATION is an intra-cellular breakdown affecting the mitochondria; in human pathology it is seen in kidney and liver in a number of febrile and toxic states, but is very hard to distinguish from post-mortem changes. In tissue-cultures and animal experiment it can be produced and the enzyme changes analysed. The organs are soft, heavy, and the details of their pattern obscured; the cells are swollen and granular; water metabolism in the cell is upset so that it imbibes excess fluid, and the visible changes follow.

FATTY DEGENERATION is a more definite affair; the fat has been shown to be derived from the mobilization of depot fat, and not from the liberation of intra-cellular fat, so this is always a change in the living cell and cannot arise *post mortem*. The cause may be either *toxic*—poisoning of the cell by known poisons, as in the heart muscle of the diphtheritic patient, or the liver of phosphorus poisoning, or it may be *anoxic*—as in the heart muscle in severe anaemias, or the liver in congestive heart failure. The disorder in cell metabolism in these cases is such that it becomes loaded with fat which it cannot break down, and this stored fat is visible both to the naked eye and microscopically. It may be seen in the kidney also when tubular metabolism is altered, in diabetes and in some stages of nephritis.

Often confused with fatty degeneration is *fat necrosis*. This is an entirely different thing, consisting of death of adipose tissue, where the other implies the appearance of fat in organs which do not normally contain it. Fat necrosis is found after injury to adipose tissue of any kind, and in the rare condition of acute pancreatic necrosis (acute haemorrhagic pancreatitis) where the pancreas is caused to digest itself by activation of its enzymes *in situ*, probably by a reflux of bile. The liberated trypsin and lipase digest the pancreas and its surroundings; the mesentery and omentum are speckled with white flecks of necrotic fat; the fatty acids are broken down and form calcium soaps, and the dead tissue and its products excite a vigorous inflammatory response.

CHANGES DUE TO DEFICIENCIES AND EXCESSES OF PARTICULAR SUBSTANCES

In considering in detail the effect of substances in the body when they are present in excess or are deficient, we must not overlook

the physiological state of the target cells and consider the substance in isolation. Pharmacological effects are usually described in relation to the whole healthy organism. In pathological states cells may become exposed to poisons which cannot reach them at all in health, as a result of breaches of surface membranes or of failure of detoxication mechanisms in the liver or elsewhere. Quite different effects may develop in particular cells if they are hyperactive, in secretion or growth for example, or actually in the stage of mitotic division. Several examples may be quoted: oxygen lack is much better endured by tissues which are cooled and rendered inactive thereby, a fact of clinical importance in the treatment of impending gangrene of limbs and in cardiac surgery; other examples are the effect of oxygen excess on the developing retina (p. 169) and that of rubella virus on the intra-uterine embryo during the first two months (p. 260). The terms excess and deficiency too must be read in relation to the demands of the body at the relevant time; the growing child, the pregnant mother, and the patient losing large quantities of protein in the urine have requirements widely different from those of the mature or elderly body.

It is more convenient to consider each substance in turn, in deficiency or excess, than to take all the excess or all the deficiencies together; the substances may be divided into extrinsic (oxygen, water, some important constituents of food) and intrinsic (the secretions of the ductless glands).

Oxygen Deficiency

Deficiency of oxygen is either *general* or *local*. The *general* causes include—

(*a*) Deficient oxygen in the air at high altitudes.
(*b*) Asphyxia: severe pulmonary emphysema.
(*c*) Anaemia: inadequate haemoglobin to carry the oxygen.
(*d*) Carbon monoxide poisoning inactivating haemoglobin transport, cyanide poisoning inactivating cellular utilization of oxygen.
(*e*) Congenital heart disease.

The effects depend on the severity of the deficiency. The function of all active organs, beginning with the brain, is depressed and death may occur within a few minutes in the worst cases. In subacute cases the brain damage results in states of confusion and coma at levels when life can still be maintained by lower centres. If a still lower degree of anoxia is prolonged compensatory physiological mechanisms and an increase in the red cells assist the patient—the haemoglobin and blood count may go up to nearly double normal

values, a process that begins after a few days at high altitudes. This is stimulated by low arterial oxygen values, but there is no guarantee that the excess haemoglobin will be saturated, and generally cyanosis is present, as is well seen in congenital heart disease when the fault is not in the pulmonary oxygenation.

Local anoxia is sometimes due to particular poisons, but is usually the result of ischaemia, oxygen lack showing up before other shortages. This is the primary cause of the death of the tissue in infarcts, and will occur with intense congestion when venous blood saturates the area, as is well shown in the liver of congestive cardiac failure. Here the venous blood fills the central part of the lobule, and the adjacent liver cells undergo fatty degeneration, so that at autopsy there is a pattern of purple congested and yellow fatty tissue (" nutmeg liver "). This is much increased by post-mortem autolysis of the central cells of the lobule.

Oxygen Excess

Although in ordinary life, no question of oxygen *excess* arises, it is possible for oxygen in excess to act as a poison, and the example chosen illustrates also the point that the state of growth of the target organ is of prime importance in determining the injury. When premature babies are nursed in an atmosphere of over 40 per cent oxygen, the developing retina and vitreous become unusually vascular, and subsequently fibrous, with the result that the babies are permanently blind (retrolental fibroplasia). This was shown by Ashton experimentally to be directly due to the excess oxygen. Other examples of oxygen poisoning occur when it is inhaled under high pressures.

Water and Salt: Deficiency and Excess

Water and salt are considered together because they are physiologically linked, and because clinically it is important to distinguish clearly whether one or the other or both are required; it can be fatal surprisingly quickly if the patient is treated for water loss by increasing salt uptake, and vice versa.

NORMAL FLUID REQUIREMENTS. The unavoidable loss of water in respiration and insensible perspiration, and the minimum amount of fluid in which the kidney in health can excrete normal waste products, amount to about 1,500 ml daily. This implies full concentrating power in the patient, and no unusual metabolism. Excess water intake is excreted by the kidney, making the urine more dilute, so that the fluid held in the body is constant in amount;

this implies an equal constancy in the salt held, for osmotic constancy is essential if cells are to function normally.

The body fluid is in three exchangeable compartments: that in the blood-plasma, the tissue fluids (together about one-third of the total), and the intra-cellular water. Tracer techniques have shown that there is continuous exchange, even when a membrane appears to be unequally permeable. Thus the cells normally have potassium ions inside them, and sodium ions outside; this barrier is not due to the inability of potassium ions to cross the cell wall but to an active adjustment of ions which requires energy.

INCREASED WATER REQUIREMENTS will be found: (*a*) when the kidney concentrating power is low, as in late nephritis; (*b*) when there are abnormal substances to be excreted, as in diabetes mellitus; (*c*) when the antidiuretic hormone of the pituitary is lacking; (*d*) pyrexia, whether arising from work in hot humid conditions or disease, will require the evaporation of a greater volume of sweat to cool the body; sympathetic overactivity will increase sweating; (*e*) increased metabolism will have a double effect—more metabolites to excrete and more cooling necessary; (*f*) loss of fluid in purgation, whether as the result of disease of the intestinal mucosa (cholera, colitis), chemical irritant poisons (arsenic), or intestinal fistulae; (*g*) the formation of large inflammatory effusions (notably in extensive burns), and the accumulation of ascites and oedema fluid.

WATER DEFICIENCY will arise when these conditions cannot be balanced by adequate intake. This may be from external circumstances (shipwreck, desert travel), or from inability to absorb water from the intestine; this includes all forms of dysphagia, neurological and mechanical, nervous and mental disease including prolonged coma, pyloric obstruction and paralysis of intestinal movement (ileus, especially with general peritonitis). Patients suffering from any of these conditions should be watched for lowered fluid intake.

WATER EXCESS is unlikely with normal alimentary tract absorption, since diminished absorption or vomiting will precede the intake of more fluid than the kidney can excrete; it may arise in renal failure if fluid is forced on the patient, and it certainly can arise with intravenous fluids, again particularly if the kidney is not fully efficient. In health such increase of plasma volume would be rapidly corrected, but it may prove the last straw for a failing heart.

The state of the patient will depend on the balance between these factors—he may be dehydrated or over-hydrated.

WATER STORAGE IN EXCESS (tissue fluid excess) can only occur if salt is retained as well; otherwise the tissue fluid would become hypotonic. It is essential that the tissue fluid should be isotonic

and of near-neutral pH. Water moving freely across the cell membrane tends to equate the tonicity irrespective of cell function; if the outside is hypotonic, water moving into the cell will rupture the cell wall which is of limited strength; hypertonic solutions outside will concentrate the cell contents to such an extent that they cannot function. The osmotic-pressure inside the cell is maintained by its proteins, and by potassium mainly as cation, phosphate mainly as anion; that in the tissue fluid, most liable to changes in concentration, by sodium and chloride. Loss of chloride is of less importance since bicarbonate is available; there is no substitute for sodium.

SODIUM LOSS is controlled by aldosterone and the deoxy-corticosteroids of the adrenal, which are continuously produced in this gland and destroyed, probably, in the healthy liver; where they are absent as in Addison's disease great sodium loss occurs in the urine. *Salt loss* as a whole can also occur from the alimentary tract (vomiting, gastro-intestinal drainage by continuous suction, intestinal fistulae, diarrhoea) and from the skin in heavy sweating. *Excess salt intake* in the food is unimportant compared with the amounts given in intravenous fluids. If there is no excretion by the kidney of such excess, however it arises, fluid will be held in the body to render it isotonic; conversely, water retention can only persist if salt is also held to maintain tonicity. Limitation of dietary intake of salt and increasing renal excretion of it (mercurial diuretics) will therefore have an effect on the amount of the tissue fluids.

Tissue fluid is normally formed as a low-protein filtrate from the arterial end of the capillaries as a result of the difference between the hydrostatic arterial pressure and the osmotic pressure of the plasma protein; at the venous end the hydrostatic pressure is such that the flow is reversed. Protein leaks to a very small extent, much increased in inflammation, and is reabsorbed almost entirely by lymphatics. Small molecules and ions can diffuse freely in accordance with physical laws and the Donnan effect. The tissue fluid compartment is the only one where expansion is possible; the cells can hold no excess, and that in the blood-vessels is limited by the volume which can be handled by the heart.

Excess tissue fluid (*oedema*) can result from: (*a*) increased hydrostatic pressure in the capillaries; (*b*) change in the permeability of the capillary wall; (*c*) insufficient plasma protein to exert osmotic pressure inside; (*d*) lymphatic obstruction; (*e*) sodium retention.

In some of the clinical conditions where oedema is seen, more than one of these factors is involved; thus in cardiac failure the venous pressure is increased and the capillary wall is anoxic because of stagnation and becomes more permeable; the ascites of hepatic

cirrhosis is associated with both an increase of portal pressure and a drop in the plasma proteins; in both these cases sodium-retaining steroids may be inadequately destroyed in the liver. Some of the oedema of Bright's disease is due to inadequate salt excretion by the kidney, in association with protein loss in the urine severe enough to keep the plasma proteins low in spite of hepatic synthesis.

It will be seen then that a patient may suffer from *dehydration* simply, with concentration of tissue fluids holding the normal amount of salt; from *dehydration plus loss of salt*; from *loss of salt* without water loss; or from an *excess of water and salt* which go together; and that such conditions can virtually arise only when renal function is impaired or the patient cannot drink normally. If a dehydrated patient is given salt, he will become more dehydrated, for the salt will either have to be excreted using up more fluid still, or it will have to be made isotonic by using up any spare water if it is not to kill him by rendering his tissue fluid hypertonic; if a patient who lacks salt is given water, conversely he will either excrete the excess water or the tissue fluid will become hypotonic. Recognition of dehydration is easy—he is thirsty if conscious, his skin lax and dry, the intra-ocular tension low, the urine volume small. Recognition of salt loss is not easy; depletion of salt does not cause thirst, but rather inertia; chemical estimation of salt in blood or urine is necessary. The position is of course usually mixed, consisting of water loss with more or less salt loss; one of the easier ways of deciding which, is to consider how the loss has come about from the history of the patient.

These physiological states are hard to recognize after death; the dry light tissues without waterlogging and the lax skin of the dehydrated can sometimes be appreciated, but there is no doubt they are overlooked and do not appear on death certificates and post-mortem reports. This is particularly true of infants, for their kidneys are much less capable of concentrating fluids, and their total volume is so small that significant fluid changes can occur quickly and inconspicuously. The term "toxaemia" covers a good deal of disordered fluid metabolism.

The various conditions that can occur under the term "heat stroke" can be summed up here. (*a*) The patient may be unable to cool himself by sweating owing to atmospheric humidity, skin disease, or having no water to drink. He will die from hyperpyrexia unless cooled artificially. (*b*) He may cool himself by sweating profusely, but be unable to make up the fluid loss. He will die from dehydration. (*c*) He may cool himself and make up the loss by drinking, but ignore the salt lost. He will develop cramps if

he does not replace the salt. Usually he will suffer a mixed syndrome containing a various amount of these elements, and the whole may be added to a sudden serious febrile illness like malaria, or arise from it in such a way that the two obscure each other; he is treated for one and dies from the other.

ACID-BASE BALANCE.' Compensation by the kidney and respiration for tendencies to acidosis and alkalosis make these states later and less important in disease than water balance; they are slower to appear and more obviously related to the illness and its treatment. Alkalosis can only occur with forced medical alkali coupled with vomiting of hydrochloric acid; acidosis in the late stages of nephritis and diabetic ketosis, and occasionally in other states of excessive fat metabolism and starvation, and after uretero-colic implants.

POTASSIUM ION. This ion, present in the body fluids in much lower concentration than sodium ions, is necessary not because of its osmotic effects but because of its role in the functioning of cells, more especially the heart and other muscles, where it is an essential for intra-cellular enzymes. Deficiency is shown by muscular weakness and mental apathy, and can arise from excessive secretion of sodium-retaining steroids which cause preferential excretion of potassium ions in the urine, and from excessive loss in the colon, an organ which excretes potassium ions and conserves sodium ions, even when there is no diarrhoea. Potassium excess is almost confined to the administration of potassium salts by mouth during oliguria, and is fatal through cardiac arrest. It may also occur from breakdown of cells in massive extravasations of blood or necrosis of tissue, when damaged kidneys cannot excrete the potassium liberated from the cells.

Deficiencies of Blood-forming Substances

IRON is normally absorbed from the upper small intestine by combination with a protein *apoferritin* in the mucosa, where it is stored as *ferritin*; the capacity of this system is limited, so that over-absorption does not occur, and iron deficiency can be made up only slowly by oral iron. The iron is transported as siderophyllin (transferrin) in the β_2-globulin fraction of the serum to the marrow for haemopoiesis. To be absorbed from the gut, iron must be in the inorganic and preferably the ferrous form, and therefore if there is achlorhydria, iron deficiency can occur in spite of adequate dietary iron. Iron loss from the body is almost confined to haemorrhage, and is thus more important in the female with menstruation and pregnancy. Iron storage occurs in the form of *haemosiderin*, which may be regarded as a supersaturated ferritin, in macrophages in the

marrow, liver sinusoids and spleen, and around any area of haemorrhage, whence it is available as required. Excess iron storage will occur in any anaemia where blood formation is depressed, but is particularly conspicuous when the cause of the anaemia is increased breakdown. The amount normally stored is considerable, and iron deficiency will not show till this is exhausted.

Although small quantities of iron are required for other respiratory enzymes, the amount is negligible.

VITAMIN B_{12} (cyanocobalamine) is also absorbed in the small gut, and again requires a healthy gastric mucosa for the secretion of the intrinsic factor (haemopoietin) without which it cannot be absorbed. Shortages of this substance may therefore arise from the absence of it or (theoretically) its essential mineral element (cobalt) in the diet, from atrophy of the gastric mucosa or gastrectomy, from steatorrhoea in which absorption in the small gut is deranged; it is stored in the liver. The anaemia resulting from the absence of the intrinsic factor from the gastric mucosa is known as pernicious anaemia, from the prognosis, fatal before the researches of Minot and Castle; or as Addisonian anaemia, from the name of the physician who first described it.

FOLIC ACID (pteroyl-glutamic acid) is essential for normal maturation of red and white cells; it may not act until converted into folinic acid. It is not absorbed in steatorrhoea.

Other vitamins (those of the B-group, and ascorbic acid), thyroid hormone and other substances have been considered to play a part in haemopoiesis, but their role is not clear.

The relation between folic acid and vitamin B_{12} is intimate; there is no response to vitamin B_{12} if anti-folic acid substances are given; progressive degeneration of the central nervous system occurs from vitamin B_{12} deficiency (p. 196) if folic acid is given to a patient already deficient in this vitamin. This suggests that the two combine in their anti-anaemic function, a further supply of vitamin B_{12} being necessary for the nervous system. The two components, vitamin B_{12}–folic acid, and iron, are related to the maturation of the stroma of the red cell and its haemoglobin respectively.

1. DEFICIENCY OF FOLIC ACID–VITAMIN B_{12}. This results in large cells, low in numbers and variable in shape, filled with adequate haemoglobin—macrocytic or high-colour index anaemia. They are also known as megaloblastic anaemias, from the characteristic cell of the marrow, the megaloblast of Ehrlich. This cell does not correspond to any in normal haemopoiesis, but has its nuclear maturation delayed while haemoglobin formation is timely, and therefore has eosinophil cytoplasm but normal nuclear form. The

usual cell at this stage is the normoblast with eosinophil cytoplasm but a pyknotic nucleus, marking the stage before the reticulocyte, the early form of the red cell in which traces of the stroma can be still demonstrated by vital staining with cresyl blue.

2. DEFICIENCY OF IRON results in a normoblastic anaemia in which haemoglobin is insufficient to fill the usual complement of cells; these may be of the normal size (normocytic), or small (microcytic); the colour index (mean corpuscular haemoglobin is a more accurate measure) is low. Such anaemias are found in iron deficiency, or after loss of blood, as soon as stored iron is exhausted.

3. ANAEMIA FROM HAEMORRHAGE. The first thing to be made up is the blood-volume. Until this is done by dilution of the blood with tissue fluid the haemoglobin concentration will be normal, and the dilution takes two days after a severe loss. The red cell number is then brought back to normal by new cell formation, the reticulocytes rising to about 10-15 per cent by the first week, and the count reaching normal by a month. If there is adequate iron, the haemoglobin may keep up with this, but if iron is lacking the cells will be at first imperfectly filled, as in iron deficiency. After about two months the effects of the most severe haemorrhage should be remedied.

It is difficult to judge by blood counts the amount of blood loss, until the period of dilution is over; clinical features are due to blood-volume loss as much as haemoglobin loss and may be exaggerated by various causes. If the blood is lost into the gut its digestion will cause a rise in the blood urea that can be of value as a guide to the severity of the haemorrhage: elsewhere the haemorrhage is usually visible.

4. APLASTIC ANAEMIA is an uncommon condition in which the marrow makes no response; the reason for this is either deficiency of substances at present unknown, or poisoning of the marrow by benzene, radiations, etc. No new red cells are formed in spite of treatment, and those present in the patient's blood die after their usual time, i.e. about 120 days. There is an associated failure to produce platelets and white cells which contributes haemorrhage and unopposed infections to the clinical picture.

5. LEUCO-ERYTHROBLASTIC ANAEMIA is the term used for states in which primitive cells of many varieties appear in a peripheral blood that is moderately deficient in red cells and haemoglobin. This is most commonly associated with multiple secondary neoplasms in the marrow.

6. HAEMOLYTIC ANAEMIAS result from the destruction of red cells at a rate greater than the usual vigorous increase in production by

the marrow will compensate. The reasons for the normal ageing and death of the red cell are not known, but two factors may be relevant to the breakdown of the cell in these anaemias—defects in the structure of the cell or its haemoglobin, and abnormal haemolysins in the serum. The first include the hereditary diseases spherocytosis and sickle-cell anaemia (see also p. 268); abnormal haemolysins are a cause of haemolytic anaemia in a number of conditions, of which erythroblastosis foetalis (p. 261) is the commonest.

Necropsy appearances in the anaemias are the result of (*a*) lack of blood, leading to pallor of organs; (*b*) excess of stored iron in haemolytic, megaloblastic and aplastic anaemias; (*c*) bilirubin excess in haemolytic and Addisonian anaemias; (*d*) secondary changes due to anoxia—the fatty change in the heart muscle; (*e*) evidence of abnormal marrow function. Ordinary haemopoietic marrow (red) is found in the vertebrae, sternum, ribs, and proximal ends of the femur and humerus in the adult; it extends into the limbs in children, and in hypertrophy of the marrow in its efforts to compensate for anaemia, notably in Addisonian and haemolytic anaemias. In aplastic anaemia, on the other hand, the trunk bones contain yellow marrow. In life the best guide to marrow activity is the reticulocyte count; these new-formed red cells normally amount to 0·5 per cent but in a marrow response may reach 50 per cent of all red cells.* If the gastric mucosa is at fault, atrophic changes may be demonstrated if post-mortem autolysis is prevented; most convincing evidence comes from gastric biopsy. This epithelium is normally in continuous growth, and the anaemia may hamper its vitality and so increase the deficiency of factors absorbed from the gut. Atrophic changes in the upper pharynx have been clinically known for a long time (Plummer–Vinson syndrome).

Until now adequate study of the mucosa of the small intestine has been defeated by post-mortem changes, and biopsy evidence is hardly beginning. There is therefore nothing useful to record about the changes in this very important absorptive mucosa, though the fatty stools of steatorrhoea have been analysed, and there is recent evidence that one type, coeliac disease, is due to sensitivity of the gut to the proteins of wheat.

Calcium and Vitamin D Deficiency and Excess

Calcium is absorbed from the alimentary tract with the assistance of vitamin D, and deficiency may therefore arise from a lack of calcium in the diet, or from a lack of the vitamin; this in turn is

* The marrow may also be sampled by films and counts made directly by aspiration of sternal marrow or the iliac crest, or by biopsy.

either supplied by the diet or synthesized in the body with the aid of ultra-violet light. Serious calcium lack is therefore seen in people living in dark cities on an inadequate diet. Calcium loss is almost entirely in the urine, that in the faeces being unabsorbed intake, a deviation of dietary calcium that is increased by the formation of insoluble precipitates from other dietary constituents. The bulk of the absorbed calcium is stored in the bone, where it is present in a form that cannot be mobilized rapidly, since to do so both cellular activity (osteoclasts) and parathormone are required. Calcium utilization (other than in growing bone) is mainly in pregnancy and lactation, when the drain of the foetus on the mother can exceed her intake and require withdrawal of bone calcium (osteomalacia). The small amount of calcium in the blood is very important because of its effect on the nerves and muscles; it is maintained by parathormone at a very steady level (10 mg per cent) without difficulty in view of the large reserves in bone, but loss or excess of parathormone is followed by a fall or rise in blood calcium, and bone calcium may be depleted by prolonged parathyroid excess.

Lack of calcium is most disastrous in the growing bone when it results in *rickets*; both the calcification of cartilage before ossification and that of osteoid tissue is delayed; the bone is soft and bends in spite of extra thickenings; the proliferation of cartilage in the growing epiphysis is not halted, so that the epiphysis is swollen. The children are flabby and resist intercurrent infection badly; mortality is high but whether this is due to calcium lack or to associated deficiency in nutrition and housing cannot be settled now, as the disease has nearly disappeared following the researches of Mellanby on vitamin D. In adults, osteomalacia with softening and deformity of bone is seen in pregnant Chinese women, and occasionally from non-utilization of vitamin D in other cases.

Lack of calcium in the blood results in the state of nervous irritability known as tetany; it may be seen in severe rickets, and occasionally following accidental surgical removal of a parathyroid gland, and in renal disease.

Hypercalcaemia may result from increased breakdown of bone—myelomatosis, or widespread secondary growths; from excess parathyroid hormone; from renal failure; from excessive intake of calcium and vitamin D, especially if coupled with diminished utilization in the skeleton—in patients recumbent in bed for a long time, with a good diet rich in vitamin D. The excess is not stored in the bone, even when the bone is normal, but is excreted by the kidney, which if healthy can deal with a reasonable excess. Prolonged hypercalcaemia results in the formation of renal calculi, and

impairment of renal function, even if normal at first; when renal failure and hypercalcaemia are combined, the calcium may be precipitated in the tissues. This is called metastatic calcification, and occurs in sites where there is a tendency to alkalosis, i.e. kidney, lung, gastric mucosa and in the media of arteries.

In hyperparathyroidism the prolonged drain from the bone leads to cysts and softening with painful crippling deformities (von Recklinghausen's disease of bone); removal of the offending parathyroid lets the bone re-form, but the renal damage may be irreversible.

There is in general a reciprocal relation between the ionic concentration of phosphorus and calcium in the blood; when the phosphate is high from failure of renal excretion, the calcium might drop to a level of tetany. Parathyroid hyperplasia then occurs to maintain the normal even at the expense of breaking down considerable areas of bone. These show fibrous tissue and irregular poorly calcified bone (osteitis fibrosa). The deformities and stunting due to chronic nephritis of this sort in childhood have caused the term *renal rickets* to be used, though there are considerable differences from rickets due to vitamin D deficiency in the clinical, biochemical and morphological changes seen.

In two other conditions abnormal calcification is seen in pathology: (*a*) Any dead tissue may be impregnated with calcium salts, which tend to change chemically into a calcium hydroxyphosphate (from whatever form they are originally deposited in) like that of bone. Two particular dead tissues show this—tuberculous caseous material, and dead benign neoplasms, notably fibromyomas of the uterus; old thrombi and old fibrous tissue (notably in cardiac valves) also may calcify. This is sometimes referred to as *dystrophic* calcification (cells abnormal, blood chemistry normal, the opposite to the findings in metastatic calcification). (*b*) Some tumours contain calcified fragments (calcospherites) without dead cells or abnormal blood chemistry, e.g. meningioma, some ovarian cysts.

Vitamin Deficiencies

The physiological action of the vitamins was worked out on animals using pure deficiencies of single substances; in human disease deficiencies are more often mixed than single. Knowledge is now so well disseminated that disease is seen in extreme poverty only, except where mental derangement, illiteracy or dietary fads interfere with a full and varied diet, or in prison populations fed as cheaply as possible. Public health measures are reducing these cases.

The effects of some deficiencies are alluded to in other chapters—vitamin B group with the nervous system (p. 196) and

anaemia (p. 174), vitamin D with calcium and the parathyroids (p. 176), vitamin K with haemorrhage (p. 127).

Vitamin A deficiency, often combined with and overshadowed by vitamin D deficiency, since the sources of both are the same, is associated with hyperkeratosis of the skin and conjunctiva (xerophthalmia, dryness of the eye); the respiratory epithelium may also undergo metaplasia. The vitamin forms visual purple, and night-blindness is a result of its deficiency.

The lack of vitamin C produces scurvy, in which weakness of capillary endothelia leads to haemorrhages in gums, periosteum, muscles and elsewhere. The cement substance between collagen fibres is poorly made; granulation tissue is weak and haemorrhagic; the process of ossification is delayed and distorted by haemorrhage and fracture at the epiphysial plate.

Vitamin E deficiency is associated with sterility in male and female experimental animals (degeneration of the seminiferous tubules in the male, resorption of the foetus in the female) but no definite evidence at present links it to any human disease.

Toxins and Toxaemia

These terms are used in general somewhat loosely, and should not be considered adequate unless (*a*) a known substance with definite origin and proved pharmacological action is involved or (*b*) when other causes of proved general depression of bodily functions have been excluded (e.g. shock, dehydration, drugs) and there is a potential source of abnormal substances in a bulky inflamed area or mass of necrotic tissue. Then there may be a legitimate inference that the body is being poisoned, but it is still desirable to analyse as far as possible the source, chemistry and mode of action of these unknown substances. When a patient looks less well, to gloss this over as " toxic " may mean missing something treatable.

Poisonous substances can be divided into (*a*) substances of known chemical structure (*b*) those of known origin and pharmacological activity, not yet chemically formulated and (*c*) those inferred as above.

(*a*) Those of known chemical structure are often highly specific in their action; the number is immense, and they are largely studied by pharmacologists and toxicologists. The methods by which the body detoxicates them are known, and chemically relatively few; the burden falls largely on the excretory and other functions of the liver and kidney, and if the substances are present in quantities greater than these organs can detoxicate, death or degeneration of the cells will result. Many of the best-known damaging agents of the liver are in this group.

Others are directly irritant to the cells with which they come in contact by ingestion or inhalation or skin absorption; many ions and small molecules have specific effects on cellular enzymes and actions (e.g. cyanide, fluoride, barium).

(*b*) Some examples of precisely known toxins, as yet chemically unformulated, have already been given as part of the effect of bacterial invasion—tetanus (p. 48), gas gangrene (p. 32), diphtheria (p. 47). In these the organism is in the body. In some cases the organism never invades the body but merely contaminates food with its toxin—botulism, a paralytic illness of the nervous system due to an organism of the *Clostridium* group, and some staphylococcal food-poisoning is of this kind. Other sources of similar poisons are the toadstool *Amanita phalloides* which resembles edible mushrooms, and certain shellfish. The importance of these sources turns largely on the resistance of the toxin to the heat of cooking; botulinus toxin is heat-labile and poisoning rare, but amanita is heat-stable and cooking is no safeguard. The pharmacological actions of these substances vary widely—botulinus affects motor nerves (especially cranial nerves), amanita the liver.

In many cases these toxins are proteins of considerable molecular weight; this explains why they are not chemically known, and why the simpler detoxication and excretion mechanisms available to deal with the first group are not available here. The antigen–antibody reaction that is the body's detoxication mechanism to these molecules is too slow to come into action to be of value against this group of toxins. Many of them are enzymes, or act directly on enzyme systems in the body.

(*c*) Little useful can at present be said about the vague toxic substances absorbed from inflamed or dead tissue or purulent exudates; the analysis of the substances present is proceeding, especially in relation to the part such substances play in the processes of inflammation; some, like breakdown products of haemoglobin, are known to damage kidney tubules and lead to tubular necrosis (p. 190).

Although in general toxins act on the more specialized tissues of the body, or at any rate their action on these tissues is more rapidly important and so more easily recognized, examples of action on connective tissues are known. A good example of the first group is the action of the simple molecule amino-acetonitrile ($CH_2.NH_2.CN$) on growing fibrous tissue and cartilage, which are completely and rapidly disorganized; in the second group of large molecule toxins those of gas gangrene acting on collagen and hyaluronic acid have already been mentioned (p. 32).

DEGENERATIVE DISEASES OF SPECIAL DIFFICULTY

Hepatic Degeneration and Repair

The position of the liver in the course of the blood-stream drainage from the alimentary tract, and its manifold metabolic functions (notably that of detoxication), render it peculiarly liable to damage by ingested substances and organisms. No organ in the body is so immediate and effective in its responses of regeneration, so that the pictures of repair and damage are often mingled in the pathological observations. For these reasons the subject is confusing; animal observations have sometimes illuminated it, sometimes led to further difficulty because the physiological, and even the anatomical, arrangements of the liver lobule are not the same in man and the experimental animals, and differ among the species used as experimental animals.

The liver lobule is described as a unit in which columns of liver cells radiate from a central hepatic vein and are supplied by a peripheral portal tract; in the human liver the lobules are not divided by connective tissue and more than one portal system supplies the columns draining into one hepatic vein. The hepatic artery and portal vein pool their blood at the outer end of the liver columns: in man the artery contributes about one-fourth of the blood but more than four-fifths of the oxygen. The consequences of occlusion of these vessels therefore differ, and are different again in animals.

Because of the immense reserve and regenerative power of the liver, the patient will survive liver illnesses for a considerable period, except when the damage is very severe. Two stages were seen and described by pathologists in the past—

1. COMPLETE NECROSIS. Rapid death from hepatic failure before regeneration is effective. The term " acute yellow atrophy " is used; the result is partly natural, but partly due to post-mortem autolysis which takes place in a damaged liver with great speed. The tissue is yellow from accumulated bile and fat; it is often blotched with red from the pooling of blood where cells have disappeared.

2. CIRRHOSIS. Damage is less severe, permitting some regeneration before death, which may be due to hepatic failure or to other causes, and may occur anywhere from a few weeks to many years later. Here the surviving liver cells have had an opportunity to regenerate, and the precise appearance will depend on three factors—

(*a*) Whether the reticulin framework of the liver has survived unchanged to permit accurate reconstruction of the lobule. If it has, regeneration will be anatomically perfect and physiologically

satisfactory; the liver may show no trace of quite serious damage, if examined months after the injury. If the reticulin is imperfect, lobules will never form properly; the nodules will be irregular, poorly supplied with blood and bile-drainage, and will be obvious anatomically and unsound physiologically; the term cirrhosis is best restricted to this state, and general terms like fibrosis, scarring, regeneration used for other changes.

(*b*) The completeness of destruction at the acute stage; if there is little of this, the regeneration required will be slight, and the new tissue will form small inconspicuous nodules. If on the other hand the cells surviving are few and widely scattered, regeneration nodules will be conspicuous, separated by areas of scarring.

(*c*) The time elapsing between the acute damage and the pathological examination. This may vary from days to years, and the maturity of the scar tissue and the size attained by the regenerated nodules will vary accordingly.

There are two important results of this: (i) the nodules in a cirrhotic liver have no relation whatever to the original lobules; (ii) the effects may not be related to the kind of agent causing the original damage (though they may be related to the quantity and certainly are related to the severity of the damaging agent).

From these two states an infinitely variable series of appearances can be described, representing degrees of damage and times of recovery, removal of the dead tissue, scarring, and regeneration; although some have been named, there is little to be gained from a series of groups; it is better to take the individual case under consideration and attempt to deduce how long the processes of regeneration and scarring have gone on, and how severe the primary damage was.

There is one thing, however, that it may well be impossible to decide, and that is the nature of the original damaging agent. You are looking not at a fire or even at the ashes of a fire, but at a rebuilding; the original inflammation may have occurred ten or twenty years ago, when the patient was a child; he may not tell a truthful history about alcoholism or vagaries of diet; he may not know what drugs he has been given. The elucidation of the cause of a human case of cirrhosis may be impossible, and too ready acceptance of a possible cause (such as alcoholism) may obscure a truth lying further in the past.

New Evidence

The new pathology of liver diseases has been partly the result of animal experiment, but even more the result of the use of biopsy

methods to illustrate the early stages of minor as well as major hepatic damage and to follow them through to the repair stage in one human patient. Combining the work on human disease and animal experiment, states of hepatic damage due to drugs, infections and dietary insufficiency have been described as follows—

1. Prolonged fatty change.
2. Acute zonal necrosis or degeneration.
3. Viral hepatitis
4. Acute massive necrosis.

1. PROLONGED FATTY CHANGE. In the metabolism of fat, the liver receives neutral fat and combines it with choline and phosphorus before it is broken down. If the liver becomes loaded with fat from overfeeding, choline will restore it to normal; if this substance cannot be formed from the diet, the deficiency will produce fatty livers. The source of the choline has been shown by tracer techniques to be the essential amino-acid *methionine*; choline and methionine have therefore been called lipotropic substances. The consequence of the prolonged fatty change is increase of fibrous tissue around the lobule spreading from the portal tract. This fine portal fibrosis around fatty hepatic lobules has long been observed in the livers of beer-drinkers and is related to the fattening nature of their " diet," to the impaired protein intake (shortage of methionine) resulting from economic inability to buy first-class protein, if he spends all his money on alcohol, and to gastritis which impairs its digestion. Cirrhosis is much more frequent in alcoholics but may not be directly and entirely due to the alcohol.

2. ACUTE ZONAL DEGENERATION* OR NECROSIS. The characteristic feature of this type of damage is that every liver lobule is affected similarly throughout the liver. The zone of each lobule affected may be the central part of the lobule (centrilobular zonal necrosis), the mid-zone, or the portal or outer zone; if the quantity of damage is great almost the whole lobule will be destroyed so that the zonal distribution is obscured. (Plate 11.)

(*a*) *Centrilobular Necrosis.* The centre of the lobule is the least oxygenated part; it is, therefore, more likely than either of the other zones to be affected by anoxia (e.g. that of congestive cardiac failure) or by poisons, which may reasonably be expected to hit hardest that part of the liver where oxidative processes of detoxication are less easily maintained. This is, therefore, the commonest site of zonal

* Degeneration (reversible) will result from minor quantities of substances which cause (irreversible) necrosis in large quantity. To avoid repetition, necrosis is used alone.

necrosis, and is known to occur as a result of: (i) congestive cardiac failure, thrombosis of the hepatic veins; (ii) the very important virus disease infective hepatitis; (iii) a considerable list of chemical poisons including that of the mushroom *Amanita phalloides*, chloroform, and carbon tetrachloride.

(*b*) *Mid-zonal Necrosis.* One example of this process is the virus disease yellow fever. The reason for the localization is obscure; the cells on either side show the minor stages of fatty change. Inclusions both in the nucleus and in the cytoplasm (the eosinophil Councilman bodies) may be seen, but the distribution of the necrosis is diagnostic. If the patient survives the hepatic damage and the secondary renal tubular necrosis (p. 190), his recovery is complete; the reticulum of the liver is unaltered, regeneration is perfect, and cirrhosis is not a sequel.

(*c*) *Portal Zonal Necrosis.* This suggests a poison arriving from the alimentary tract. It is found in ulcerative colitis, and, one of the most severe fatty degenerations, in phosphorus poisoning.

Zonal necrosis is regular in the population exposed to the cause, predictable, unaffected (except to a minor degree in severity) by diet; the whole liver is equally affected, and, except in the worst cases, healed rapidly from the surviving unaffected part of the lobule.

3. INFECTIVE HEPATITIS is now known to be the result of infection with a virus transmitted by way of the alimentary tract from case-to-case, only humans being affected. This has been shown by passage through a series of human volunteers, and by the development of antibodies. For eighty years it was taught that the disease resulted from catarrh at the ampulla of Vater, and it was called catarrhal jaundice. The infectivity and the incubation period were proved by an English doctor in general practice, Dr. W. N. Pickles, who found it possible in a country district to demonstrate that the incubation period was about thirty days; hospitals and universities in towns had not the advantages of semi-isolated communities to show this. The companion disease serum hepatitis, possibly the same virus and certainly a closely related one, was known in medical circles as a complication of various forms of drug treatment, notably that of arsphenamine derivatives for syphilis, and gold for rheumatoid arthritis. It was shown in 1942 that while the disease did not associate with any particular drug it did associate most certainly with indifferent sterilization methods for syringes and needles, and was particularly associated with injection materials containing human serum, notably the plasma pooled from many donors that was such a useful substitute for blood for transfusion in war-time

conditions. The disease differs from ordinary infective hepatitis in two main points, a much longer incubation period (about 100 days) and a tendency to produce a more serious illness. In both diseases liver biopsy has shown the same necrosis in the acute stages, often centrilobular, but sometimes in other parts of the lobule, with preservation of the reticulum pattern, so that the regeneration which follows is orderly and usually complete. Prolonged subacute attacks do occur and lead to cirrhosis: an occasional case, more often in pregnant women and debilitated populations, goes on to complete zonal necrosis and is seen at *post mortem* as acute yellow atrophy.

4. ACUTE MASSIVE NECROSIS. This has been shown in animals to occur from dietary abnormalities alone, without any known toxin or infection. The important deficiency is in the sulphur-containing amino-acids cystine and methionine (which occurs twice in connexion with liver function).

It has been suggested that the cirrhosis so common in the poorly nourished South African native is due to similar dietary defects (*Kwashiorkor*); it must, however, be remembered that these deficiencies are not pure but complex, and parasitic diseases as well as other infections are rife. The incidence of cirrhosis in these natives is, however, striking, occurring, with its sequel primary carcinoma of the liver, far more commonly than in Europe and America, and being found even in children.

Massive necrosis is also found from the use of some drugs (atebrin and cinchophen) and contact with toxic chemicals (TNT in shell factories). It is characteristic that the individuals affected are only a few in the group at stake; the incubation period is long; possibly dietary or other personal factors determine whether the individual is sensitive or not.

CIRRHOSIS: THE ESTABLISHED STATE. When (or even before) the primary toxic agent has been disposed of, regeneration of surviving cells and fibrosis in the areas of complete destruction proceed. The patient's future is determined by two things—the efficiency of the regenerated tissue, together with any original unaffected liver there may be, to carry out the normal hepatic functions; and the effect of the fibrosis on the portal circulation, the obstruction being partly due to the collagenous tissue, partly from the pressure of the growing nodules of regenerating tissue.

At this point it is desirable to bring together all the conditions which are associated with the term cirrhosis. These include—

1. Regeneration following types of hepatic damage, sometimes referred to as multilobular, Laennec, hobnail, or portal cirrhosis.

2. Biliary cirrhosis. A straightforward post-inflammatory fibrosis

following prolonged suppuration in the biliary tract; there is little hepatic destruction or regeneration, but often pools of extravasated bile. Hanôt's cirrhosis may be regarded as a sub-group of this in which the obstructing agent is not found.

3. Cardiac cirrhosis. Fibrosis following prolonged congestive cardiac failure with anoxic centrilobular degeneration. Abundant fibrous tissue is found, regeneration is variable.

4. Acquired syphilitic cirrhosis. In tertiary syphilis there may be gummata in the liver; these form massive scars, but there is no abnormality in the rest of the organ.

5. Congenital syphilis on the other hand leads to a scarring so fine that the fibrous tissue appears to surround every individual cell; the liver is densely hard—flint-stone liver, pericellular cirrhosis. This is a general serious disease; the liver is uniformly affected; hepatic failure is well marked, and the patient dies before any nodular regeneration can occur, or obstructive symptoms develop in the portal circulation. Acquired syphilitic cirrhosis is, on the contrary, largely an affair of portal obstruction.

6. Parasitic cirrhosis. Fibrosis in portal tracts round veins containing Schistosoma and Clonorchis. " Pipe-stem " cirrhosis.

Effects of Cirrhosis

1. HEPATIC INSUFFICIENCY. The cirrhotic nodule of regeneration by definition has an irregular anatomical build, and it is always more or less physiologically inefficient, shown in histological samples by the presence of fatty changes from anoxia, and retention of bile; these give the liver the tawny colour that is literally translated in the name " cirrhosis." The reserve power of the liver carries the patient along till pretty near the end before hepatic failure is well enough marked to detect by clinical or chemical examination.

Tests of hepatic function are numerous. Observations on the efficiency of excretion of bile-pigments may show failure before clinical jaundice is present, and excretion of alkaline phosphatase into the bile may fail, so that the serum levels of this enzyme and of bilirubin are raised. These are affected particularly in biliary obstruction.

This bilirubin, having been handled by the liver, is in the conjugated water-soluble form that gives a direct van den Bergh reaction; the fat-soluble form in which bilirubin is present in the plasma gives this reaction only indirectly, after treatment with alcohol to facilitate its solution; both are absorbed on albumin.

The synthetic functions of the liver parenchyma are assessed by the estimation of the plasma proteins directly, or indirectly by the

flocculation effects of the globulins—not made in the liver and so not reduced (e.g. the thymol turbidity test). Other tests are directed at detoxication, e.g. of hippuric acid. These are not affected by biliary obstruction but are related to the amount of damage of the hepatic cells. By the use of several of these it may be possible to distinguish between parenchymatous liver disease and that which is secondary to bile-duct obstruction, and to gauge the progress of the damage in a series of repeated tests. Liver biopsy is safe except in the presence of deep jaundice and is of particular use in clinically puzzling enlargements of the liver without jaundice, allowing for the sampling error when a large organ is judged by a small fragment of tissue chosen at random. In the late stages of hepatic failure a low blood-sugar and blood-urea are found; the latter, reflecting the impaired metabolism of protein, is related to the accumulation of ammonia in the blood which is one cause of hepatic coma. This ammonia formed in the gut is normally used by the liver in urea synthesis; it is side-tracked into the main blood supply unchanged when there are large porto-systemic anastomoses and poorly functioning liver cells. It may be increased by large protein diet (including in this the absorption of large gastric haemorrhages) and by ammoniacal drugs. The blood amino-acid level is raised, the amino-acids excreted in the urine, and in the worst cases the most insoluble of them may form crystals in the urine (cystine, leucine and tyrosine).

2. PORTAL OBSTRUCTION. This leads to dilatation of the portal capillaries so that more of the pressure in the arteries is available to push the blood through, and so to open up venous channels linking the systemic veins with the portal: notably those in the mucosa of the oesophagus, those round the umbilicus, in the retroperitoneum, and the haemorrhoidal veins. Congestion there is usual and varicosity may be observed clinically; the really important complication is severe haematemesis which is a common cause of death in patients with established cirrhosis. The reservoir function of the spleen is increased and this organ more than doubles in size; the anaemia of patients with cirrhosis (Banti's syndrome) may be due to hepatic dysfunction, intestinal absorption defects or to over-activity of this organ. There is often ascites, due to interference with the steroids controlling sodium metabolism and increased exudation from congested capillaries, assisted by a low plasma protein.

It will be seen that the symptoms resulting from cirrhosis fall into two main groups, with different possibilities for treatment; surgery may improve the obstruction in the portal circulation but will only indirectly benefit hepatic cellular economy.

Special Degenerative Conditions in the Kidneys

In this group the distinction between inflammation and degeneration shrinks to vanishing point: the changes are the result of vascular and toxic processes on the kidney with the consequent removal and replacement of the dead cells.

Preliminary Points

The renal glomeruli are incomplete both functionally and anatomically at birth, and development proceeds until the age of two. After this the glomeruli can no longer multiply and can only regenerate to a limited extent; but the tubules can increase in length and also regenerate with considerable effect. The ease with which they do so and the frequency with which tubular cells can be found in normal urine suggests that this cellular turnover is a normal process; it is possible that the same is true of the glomerular epithelium.

The blood supply of the tubules is derived from the efferent stream of the glomerulus belonging to the tubule; apart, therefore, from agents which harm the tubule itself, it is liable to a double effect from the glomerulus—the filtrate on the " urine " side of the tubule cell and the blood on the outer side are both provided by the glomerulus, and both are involved in tubular function.

It has further been shown that in the rabbit the blood supply of the outer two-thirds of the renal cortex may be cut off and the blood entering by renal artery largely shunted directly into the renal vein in conditions of shock when conservation of the blood-volume to the most essential parts of the body is required. Massive cortical necrosis, symmetrical in both kidneys and sparing the medulla and the glomeruli nearest to the medulla, has been seen in somewhat similar cases of shock (particularly obstetric) in the human, and suggests that this or a similar ischaemic mechanism is also possible as a result of spasm in the arterioles of the human kidney. To this possible vascular damage some of the consequences of shock in the human are attributed; the vascular effect will be greater on the actively metabolic tubule cell than on the filtering cells of the glomerulus.

Degenerative changes in the kidney may result from—

1. Ischaemia—gross infarction; infarction of small units.
2. Toxic substances of known constitution.
3. Inferred toxic products.

To all of these is added further trouble owing to the liberation of pressor substances by *any* damaged kidney. These substances,

acting in a somewhat obscure manner requiring the adrenals as intermediates, bring about both spasm and structural changes in small arteries which produce widespread ischaemic changes in the body, none more conspicuous and important than those in the kidney itself, and often leading to death from renal failure by combined cumulative effects over a relatively brief period.

The effects of any such toxic damage will be determined by the primary extent—acute renal failure if severe enough; by the compensation of overwork by other nephrons; by regeneration and physiological alteration in surviving tubules; and by the rate and intensity of hypertensive effects. The picture of the kidney at autopsy—but not necessarily its physiological efficiency—may be modified by secondary fibrous changes, by haemorrhages, or by the deposition of abnormal substances in the tubules and the interstitial tissue.

1. ISCHAEMIC CHANGES. An occasional case may be seen in which the stenosis is in the main renal artery and the consequent atrophy affects the whole of the kidney, but in general the consequences of ischaemia in the kidney are patchy, and gross scars in an otherwise normal kidney arise either from infarction or purulent infection ascending from the renal pelvis (pyelo-nephritis). Gross infarcts are among the most characteristic of arterial infarcts, the pyramidal area of supply of the blocked vessel undergoing coagulation necrosis and later forming a deep scar retaining something of the outline of the square base of the pyramid. When there are many small infarcts throughout the organs the alteration in their normal smooth contours is striking (" the mouse-eaten kidney "), but in all these kidneys the renal reserve is great enough to maintain perfect function in spite of the scarring. Even when the individual areas of infarction are of microscopical dimensions and very numerous, the same applies; it is very unusual for ischaemic damage to be so widespread and uniform that it causes renal failure.

There is one important exception to this, the renal changes of *malignant hypertension*: this severe form of hypertension shows the fibrinoid degeneration of the arterioles very clearly in a number of glomeruli, the neighbours of which are normal histologically, but the kidney as a whole is in failure, and so much so that the patient dies before any severe degree of scarring or regeneration can occur. The kidney, therefore, may look very nearly normal apart from the congestion of heart failure and scattered petechiae and splinter haemorrhages in the cortex marking the sites of fibrinoid arterial necrosis. It is likely that there are severe functional changes in the arteries which do not show the fibrinoid changes. This leads to the

paradoxical position where the kidney in a case of benign hypertension may be most seriously deformed and scarred, so that a layman would be sure it was grossly diseased, and yet the patient does not die of renal failure (unless there are additional factors such as prostatic obstruction); whereas the fatally damaged kidney of malignant hypertension is so nearly normal that it may be overlooked by a pathologist, though usually the petechiae can be seen and a degree of scarring and regeneration make it slightly nodular; malignant hypertension rarely lasts long enough to give a grossly scarred organ. As so often, a warning must be given about two conditions being often added to each other; chronic pyelonephritis with severe renal scarring may well be the cause of a malignant hypertension and the kidney show at *post mortem* the changes of both processes.

2. TOXIC CHANGES DUE TO KNOWN SUBSTANCES. That certain substances can act directly on the tubular epithelium has been known for years, the diuretic effects of mercury being an example. Certain poisons of this sort (mercurials and heavy metals generally, phenol, carbon tetrachloride) are known and can be shown experimentally to damage the tubular epithelium; fatal cases in human pathology show a direct effect on the tubules, sometimes the first and sometimes the second convoluted tubules being more affected, so that the old name "lower nephron nephrosis" is less satisfactory than *acute tubular necrosis*. The tubular cells show the usual changes of dying and degenerating cells, desquamate into and may block the lumen, and are surrounded by regenerating surviving cells and inflammatory cells removing the debris. During this active poisoning phase, the secretion of urine is held up, and the patient becomes anuric. The succeeding phase is one of gradual return to normal function by the regenerating tubules, the dead cells being in part excreted and in part removed by the inflammatory cells. The course of this process is marked by the return of urine flow, at first dilute and copious; but as new tubule cells are formed and become functional the power of concentration returns. Since tubular regeneration is efficient, this results in complete recovery, if there are no added lesions in other organs and if there is no injudicious treatment in the period before the kidney can take over efficient osmoregulation again. It may be necessary to tide the patient over a few critical days with artificial kidneys.

Clinically similar pictures resulted during the war when patients were rescued from crushing injuries to muscles; recovery from the immediate injury was complete, but some eleven days later the symptoms of renal failure appeared, exactly as in patients who have

only a single kidney and it is removed by mistake. The histological picture, if these patients died, was very like that of poisoning, but the possibility arose that ischaemic shunt mechanisms were also operating, as well as inferred toxins from the damaged muscle. Other causes of the same syndrome were incompatible blood-transfusions, and the haemolysis of large quantities of blood in blackwater fever in malaria; necrosis of muscle tissue from tourniquets left on in error; retained haemorrhage in the uterus, and necrosis of myometrium from sepsis; and the hepatic destruction of Weil's disease, yellow fever, and acute yellow atrophy.

At present the responsibility cannot be divided between shock ischaemia and toxic effects in these conditions; but the block in the lumen of the tubule is the consequence of the damage to the tubular cells, and not as was once thought the result of precipitation of insoluble haemoglobin products in the tubular lumen with secondary effects on the cells. The most important point about this kind of damage to the kidney is that it is essentially completely recoverable if the patient can get over the week or two in which the tubular damage is undergoing repair.

3. INFERRED TOXIC CHANGES. The forms of renal impairment collectively known, after one of the most distinguished of all early physicians, as Bright's disease show various stages of what can be interpreted as inflammatory, vascular and degenerative changes, in which no real suppuration occurs and in which no organisms have ever been found. The association of some cases with throat infections has led to the suggestion that they are allergic responses like those described in rheumatic carditis (though the evidence is less complete and does not cover all cases), due to an inferred toxic product from the patient's own body (p. 93).

Exactly the same difficulties that made the study and terminology of hepatic disease difficult and confusing have occurred again here. The morbid anatomy was built up on a single examination only of each case, at the end of a protracted illness in which damage and repair were mixed and of which the important pressor element was not known till the 1930s. A few cases were seen in the early stage of the disease but there was no proof that they were characteristic of the cases which survived till the late stages, and the evolution of the process was rather unsatisfactorily worked out from a series of cases. We can expect in the next decade very considerable enlightenment from renal biopsy, just as we have from hepatic biopsy in the last decade, and much that is at present confusing and debatable will be established. The practice has been proved relatively

safe and a new pathology of the kidney will soon be built up; until then, it is advisable to regard details as *sub judice*.

Two main forms of the disease were separated by Ellis from observations of more than 600 cases over nearly thirty years, an experience that is so unusually extensive that his observations demand respect, even if they have not received unqualified acceptance. No other classification has won any acceptance at all, and it has been said that there are as many classifications as clinicians. Since the Ellis classification has clinical application it will be taken up here, but it must be said that the histological details are not completely published and may require modification from renal biopsy studies.

Ellis described two very different sets of patients. In Type I, young patients with a preceding streptococcal infection developed abruptly a nephritis with haematuria, very nearly all recovering completely, and those that did not having a long illness; in Type II, people of any age with no preceding infection were found (often on routine examination while apparently perfectly well) to have albuminuria; this insidious illness progressed through an oedematous phase to an early termination in renal failure in the great majority. Although some apparently intermediate cases could be found, the majority fell clearly into one or other group, provided good clinical evidence was available for the whole course of the disease; separation of those already dying in uraemia might be impossible.

The clinical contrast between these two types is usually clear if the whole story is available; the pathology is not, partly because the opportunities for examination are unequal. The good prognosis of Type I means that post-mortems will be few, and will occur only in unusual cases; but these are the very cases that will be seen in the hospitals. The course of Type II is such that more adequate examination is available, but the disease is much less common.

Experimental evidence is unsatisfactory, though antigen–antibody destruction of the kidney has been achieved; it has been suggested that with certain organisms the antigenic similarity is with the glomerular tuft, in others with the capsule, and that the streptococcal antigens have chemical similarity and so lead the patient to make antibodies to his own kidneys.

In all forms of Bright's disease it is characteristic that all the glomeruli are more or less equally affected throughout both organs. The histological forms of the destruction differ in the two types—

Type I. Proliferation occurs in the epithelium of the glomerular tuft (Plate 12) so that it swells to fill the whole of Bowman's capsule. An acute inflammatory polymorphonuclear response may be seen in the glomerulus and in the lumen of the tubules. Examinations in

the early stage are very few, however, and occur when the sudden hypertension that occurs in these patients leads to death from left ventricular failure, or from oliguria. In another group, small numerically (4 per cent), the condition progresses steadily through an oedematous stage in about six months to death from renal failure; these make up a large proportion of deaths in hospital in the subacute stages of nephritis, and show a characteristic proliferation of the epithelium of Bowman's capsule rather than in the tuft ("crescent formation"). The reason for this is obscure: the suggestion that it is organization of haemorrhage into the space is unlikely as there is no iron pigmentation; it might be well to consider this as a further type of nephritis rather than as a member of Type I.

Type II. The glomerular lesion is at first invisible, but physiological permeability is clear, since these patients have, to begin with, albuminuria and nothing else. After a few months to years, thickening of the basement membrane of the tuft can be demonstrated (Shaw Dunn) and this becomes increasingly conspicuous. The tuft becomes broken up into lobules, hyaline masses form in the periphery (focal necroses) and vascular granulation tissue moves in from Bowman's capsule forming adhesions to the tuft and finally destroying it completely. During the earliest stages, when the glomerular changes are not visible, changes in the metabolism of the tubules which have albuminous fluid in the glomerular filtrate become conspicuous; they are heavily loaded with lipoid (visible to the naked eye at *post mortem* as yellow streaks), and with hyaline protein droplets (grey streaks). For these reasons the disease was at first thought to be a tubular rather than a glomerular defect.

Once the acute changes are over the additional factor of pressor substances derived from damaged renal tissue comes in. In 1938 Goldblatt showed in dogs that ischaemic renal tissue generated a pressor substance (possibly related to the "renin" of Tigerstedt) and that the hypertension resulting from this could take either the benign or malignant phase. This work was extended by other workers in the rat, and it was shown that the hypertension could be abolished by removal of the damaged kidney.

This experimental work has been shown to be valid in humans, particularly where the renal damage is unilateral as it may be in inflammatory disease of the kidney; hypertension both of the benign and malignant types has been found in people with a single kidney affected by chronic pyelonephritis, and the removal of this useless organ has reversed the hypertension. In Bright's disease the lesion is invariably bilateral and diffuse, and does not lend itself to surgical approach; but the mechanism provides an explanation of

the constant association between chronic renal disease and hypertension.

The rate and intensity of this secondary change vary; in Type I it tends to be present in the early stages, and again after decades of quiescent chronic nephritis; it is more frequently of the malignant variety. In Type II it comes on sooner after renal damage is established and is of a more slowly progressive type. In both types, once it has set in it confuses the picture by adding a sporadic ischaemic effect to the original diffuse changes; it marks a start for the patient of progressive renal failure, and for the clinician the beginning of chronic nephritis with uraemia. Considerable tubular hyperplasia occurs from surviving nephrons and contributes to the excretion of urea—this is one reason for the " granularity " of these kidneys, another being fibrosis. But this does not compensate for the destruction of the rest of the kidney. Once this stage has set in it is not easy to distinguish the two types, apart from the clinical history; both at the bedside and at necropsy the pictures are alike, and that of malignant hypertension (p. 149) in renal failure is again very similar. It is therefore easier to speak of the clinical state of *uraemia* and *chronic nephritis* than to discuss the types from which the disease started; unfortunately for the patient it makes no difference. The syndrome uraemia includes not only renal failure, with retention of urea and other substances in the blood, but symptoms due to hypertension and heart failure; unless it arises from urinary obstruction or infection which can be treated, it implies renal damage so diffuse that it is irreversible. The term " extra-renal uraemia " is used when the retention of urea is due to dehydration, cardiac failure, or other causes outside the kidney; this organ is undamaged although physiologically functioning at a disadvantage, and if the dehydration or cardiac failure are successfully treated, the kidney can recover.

Degeneration and Allied Changes in the C.N.S.

Just as in the inflammations, there are sufficient differences in the reactions of this tissue to make it essential to consider them separately. The units to be considered are (*a*) the neurones (*b*) their axons (*c*) the myelin sheaths, maintained by the oligodendroglia inside and the cells of the neurilemma (sheath of Schwann) outside the C.N.S. (*d*) the other glial cells. It will be remembered that the myelin sheath depends on the presence of an intact axon, and the function, though not the structure, of the axon depends on the existence of the myelin sheath; both may regenerate outside the C.N.S. if the neurone is healthy, but neither regenerates effectively inside the C.N.S. The myelin, lying outside the axon, is either more delicate or more

exposed, and tends to suffer first; the convenience of this for study of the effects of injury has been alluded to already (p. 98).

Normal Maintenance of these Structures

The non-regeneration of the neurone or myelin following injury is not evidence that they remain unchanged throughout life; turnover studies with isotopes have shown that both the nucleoprotein of the neurone (phospho-protein studies with ^{32}P) and the lipids (phospholipids studied with ^{32}P and fatty acids with deuterium) show the same order of turnover as other tissues, admittedly not up to the fastest. There is therefore steady replacement of chemical material in the C.N.S. though no large-scale repair. The agents bringing about defects in this system are—

1. Deficiencies: oxygen; glucose; vitamins and trace elements.
2. Toxins: known chemical substances; bacterial toxins; other suspected noxious substances.
3. Demyelinating agents; antibodies and unknown.

DEFICIENCY OF OXYGEN. The oxygen requirements of the brain are of the highest, and only a very brief deprivation of blood is tolerated by the cortex, e.g. the abrupt unconsciousness of Stokes-Adams attacks when the heart ceases to beat for a few seconds. Less than 1 min. of anoxia will extinguish normal cortical activity, though survival is possible after a much longer time, and the medulla will function after nearly ½ hr.

If the oxygen lack is rapidly fatal, whether it is due to low oxygen tension in the air or to carbon monoxide, no structural changes are visible in the brain after death, or they are obliterated by post-mortem artefacts; if however the patient survives a few hours, patchy loss of cortical neurones may be seen histologically, and softening, shrinkage, and discoloration with small cysts and rarely petechiae in the corpus striatum and cornu Ammonis. Similarly only the grossest toxic changes in the cells can be distinguished from post-mortem changes, which are very rapid, and may be well advanced in the hour or two that is bound to intervene in human cases between death and autopsy; even with animals care is necessary to separate them. The multiple cysts that form in the brains of the dead who are not refrigerated are sometimes a source of difficulty; they are due to invasion *post mortem* by gas-forming bacteria.

Where the ischaemia is local and survival for a time occurs, the findings will be those of infarction with colliquative necrosis; there is yellow opacity from microglial accumulation, brownish staining from blood in the phagocytic microglia; in the end the shrunken,

pale, brownish, partly cystic area is encapsulated by fibrils from astrocytic glia.

DEFICIENCY OF GLUCOSE. Because there is no stored glucose and no good alternative source of energy, the most immediate symptoms of hypoglycaemia are cortical; coma may ensue, after misleading symptoms rather like those of alcoholism, and unless rapidly treated may prove irreversible. The subject is linked up with insulin deficiency and excess (p. 203).

VITAMIN DEFICIENCY. Lack of the vitamin B group is clinically usually a mixed deficiency as most deficiencies are, but the components recognized are—

Vitamin B_1 (thiamine) deficiency (beri-beri). The vitamin acts as a co-enzyme in the pyruvate cycle; no structural changes are visible in the brain except in *Wernicke's haemorrhagic encephalopathy*, an uncommon complication of a wide range of conditions, mainly gastric, including chronic alcoholism. Changes also occur in the peripheral nerves, with partial demyelination, and in the heart muscle.

Vitamin B_2 (Nicotinic Acid) Deficiency (pellagra). Again the vitamin is an essential part of enzymes related to intra-cellular oxidation. In disease the condition is partly due to lack of associated vitamins, in particular riboflavin, and shows hyperkeratinized pigmented skin, ulceration of the alimentary tract, and demyelination.

Vitamin B_{12} (Cyanocobalamine) Deficiency (subacute combined degeneration of the cord). There are associated defects in the maturation of the red blood corpuscles (p. 174). Patchy demyelination is found in the posterior and lateral columns of the spinal cord, especially in the thoracic region; spongy areas of destruction can be seen histologically including the axons, and with no surrounding inflammation or gliosis; there may be slight gliosis after treatment. The peripheral nerves are similarly involved.

DEFICIENCY OF TRACE ELEMENTS. Lack of *copper* is of theoretical rather than practical interest, in that in Australia a symmetrical cystic degeneration causing paralysis in lambs was shown to be due to lack of copper in the soil, and arrested and prevented by copper administration. The copper as a trace element may be compared to the *cobalt* in vitamin B_{12}. Excess of copper and its abnormal metabolism is related to the rare Kinnier-Wilson's disease (hepatolenticular degeneration); but the real importance of trace elements is as a possible cause of many toxic-deficiency diseases we cannot at present explain.

TOXINS. The borderline of pharmacology rather than pathology includes alcohol and the anaesthetics; linked more to structural change are the demyelinating anti-cholinesterase group, including

tri-o-cresyl phosphate and the fluorophosphates, though the detail of how they act is not complete; the acute specific poisoning of the ganglion cells of the retina by methyl alcohol; and the more chronic poisoning of the neurones of the basal ganglia by manganese.

Many toxins act on the peripheral nerves; these can recover from insults, and are better studied in the living than pathologically, especially as the only reaction visible is demyelination, which does not vary with different causes and which in any case represents only the most severe damage; functional changes are visible morphologically only when extreme. Known causes of peripheral neuritis include: diphtheria toxin, motor and sensory, symmetrical and fairly complete; diabetes, sensory only; alcohol (confused by the possibilities of deficiency in vitamin B); and lead, which acts on the muscles rather than the nerves, though there is an acute lead encephalopathy due to its action on the brain.

Central Nervous System

Certain changes seen frequently in the brain of the elderly can at present only be described as age degenerations, since the chemical basis is unknown. These include the senile cortical atrophies, with progressive disappearance of neurones, and degenerate neurofibrillae and increase of lipofuscin pigment in those that survive; and the precipitates in the ground substance of material staining with silver that are referred to as senile plaques. Of histological importance only is the occurrence of haematoxyphil rounded bodies known as corpora amylacea, which can be mistaken for significant lesions if they are not known as regular scattered conspicuous objects beneath the ependyma and pia in sections from the brain and cord in the elderly.

Two particular disease entities of great clinical importance belong to the heading of simple atrophy of neurones, without any inflammatory changes. They are *progressive muscular atrophy* (*motor neurone disease*) in which the motor neurones in both brain and cord disappear, with consequent progressive paralysis; and *paralysis agitans* (*Parkinson's disease*) in which the cells of the substantia nigra are affected, leading to disorders of movement and emotional expression but leaving the intellectual functions unimpaired—a point important to realize in conversing with the sufferers who are well aware of their condition and whose vacuous expression is entirely misleading. A few cases of Parkinsonism are due to the late stage of a virus disease, encephalitis lethargica, and a few more to manganese poisoning, but the agents causing the majority of cases of this common condition are still unknown.

Apart from ordinary infarcts, two consequences of arterial disease are diffuse cerebral damage in the elderly from multiple small patches of gliosis of microscopical dimensions, not giving any definite neurological signs; and the apoplectic stroke or cerebral haemorrhage, occurring in the basal ganglia and often fatal from gross bleeding into the brain, which is a common event in any hypertension. If the patient survives, the haemorrhage is absorbed leaving a comparatively small cavity lined with brown iron-containing microglia. In the fatal cases the whole area is so destroyed by the bleeding that even now the exact cause for the rupture of the arteries in this very common condition is not known; atheroma, preceding small infarction, and microscopic aneurysm have been suggested.

Demyelinating Diseases

The dependence of the myelin sheath on the presence of an intact axon has been alluded to already, and several toxic causes of demyelination have been mentioned. In a further group of cases the demyelination does not follow the distribution of tracts as does that which is consequent on axon loss, nor has it the diffuse distribution of many toxic and deficiency processes. Two patterns are recognizable: (*a*) perivascular (*b*) irregular.

(*a*) PERIVASCULAR DEMYELINATION (Plate 10*b*). Following measles, smallpox, vaccination against smallpox, varicella, and anti-rabies inoculations, cases from time to time of severe nervous disease were observed; these were called encephalitis until pathological examination showed that a well-marked perivascular patchy demyelination, but only slight secondary inflammation, was present. The vessels were not thrombosed, though there was sometimes punctate haemorrhage around them (haemorrhagic leucoencephalitis); no virus could be shown by passage, nor was there as much perivascular cuffing as in virus infections or the encephalitis following mumps. The disease produced was similar, whichever of the preceding infections started it, and it appeared in the second week of the infection at the time when antibody formation was becoming prominent.

The key probably lies in the anti-rabies inoculation, when material derived from nerve tissue is injected and can act as an antigen; similar perivascular demyelination can be produced experimentally by subcutaneous inoculation of brain tissue, though there are complexities which make it an unusual type of reaction. The survivors do not go on to progressive demyelination.

(*b*) IRREGULAR DEMYELINATION (Plate 10*c*). Disseminated sclerosis

(also known as insular or multiple sclerosis) is a relatively common disease in which patchy irregular demyelination of the brain and cord is found, progressing slowly and often in distinct episodes until the patient may be completely paralysed. Although the small early lesions may be symmetrical and perivascular, the finished process is not so; the foci may be few or very numerous. The oligodendroglia are absent in the plaques, and the myelin sheath is removed by the microglia; subsequent gliosis is responsible for the hardness of the grey plaques found at necropsy which have given the disease its name. The axis cylinders passing through the plaques may persist unchanged, even if they do not function; there is unexpectedly little degeneration propagated along the tract; similarly neurones included in the plaque are unaltered. The plaques are perivascular only when small and the vessels in them are normal, without thrombosis. The peripheral nerves are normal and there are no changes in the rest of the body. The course is remittent with very variable speed of progress and much affected by intercurrent events.

No definite statement can be made about the cause, though infection of any kind can be ruled out. No experimental animal has been affected. The possibility of an allergic basis has been raised, on analogy with the perivascular demyelinations and on the frequency with which the sufferers show other allergic manifestations; but the patches of disseminated sclerosis tend to spread, while those of perivascular demyelination do not, and there is no clinical association between the two conditions or relationship to known causes of demyelination. The absence of oligodendroglia may explain why the patches do not remyelinate, and the cells may be the first to be lost. The conditions known as Schilder's and Devic's diseases are probably varieties of disseminated sclerosis, and there are other forms too rare to include here.

Biochemical Disorders of Cerebral Function

Where no structural changes are demonstrable, these are likely; one of the best examples is the inherited form of mental defect where there is an arrest in phenylalanine metabolism—phenylketonuria. Research in this field is beginning.

ENDOCRINE DEFICIENCY AND EXCESS

The manner in which these arise is sometimes obvious—deficiency in iodine in the food will clearly impair the formation of the thyroid hormone which contains iodine; infarction of the pituitary will destroy the secreting cells; overgrowth or benign tumours (p. 221)

of endocrine glands may increase their secretion. In other examples (diabetes mellitus for example) the fundamental cause is still open to research.

Simple examples, in which the effects are deducible from the physiological action of the gland hormones, include the parathyroids, where the effects on the blood-calcium of removal or overgrowth have been described (p. 177); and islet-cell tumours of the pancreas have effects exactly comparable to an overdose of insulin.

The pituitary and the thyroid : thyrotropic and thyroid hormones

The thyroid is controlled by the thyrotropic hormone of the basophil cells of the adenohypophysis; deficiency in this hormone in pituitary cachexia (Simmonds' disease) leads to hypothyroidism; excess of it, arising from causes as yet unknown, produces increased size and activity of the thyroid, and protrusion of the eyeballs as a side effect (exophthalmic goitre). The thyroid hormone, elaborated in the acini in response to the pituitary, is normally stored in those acini in the form of thyroglobulin, from which it is fed back into the blood as required. If this hormone is not present, there are changes in the skin and hair of the patient, in his metabolism, which is exceedingly depressed, and in his mental activity; the reasons for the absence of the hormone may be congenital absence of the thyroid, absence of iodine in the diet or interference with its absorption by bacterial or other dietary factors, or absence of the necessary pituitary stimulus. If the deficiency arises in infancy, the resulting state is known as cretinism, if in adult life as myxoedema, and thyroid administration may correct much of it. Where the cause is iodine lack, replacement of this may be all that is required; in these patients, the pituitary hormone acts in excess so that the gland enlarges and its acini become filled with a thyroglobulin in excess, to make up for the lack of iodine in it (diffuse colloid goitre). Some diffuse nodular goitres may be hyperplasia due to prolonged less severe iodine lack (Selwyn Taylor).

Excessive thyroid activity does not appear to arise spontaneously in the gland, but is associated with pituitary overstimulation, so that the increased metabolism of Graves' disease (exophthalmic goitre) is associated with exophthalmos. The gland is large and vascular, the epithelium overgrown to such an extent that it bulges in papillae into the acinus, and so much more colloid is withdrawn than made that the colloid is poorly stained and vacuolated. This overactivity may be temporarily damped down by giving excess iodine, which enables the acinus to store its colloid; it may be more permanently blocked by the thiouracil group of drugs which prevents

the synthesis of the hormone. Surgical removal of the overactive gland may be necessary, since treatment of the underlying pituitary defect is not possible.

The physiological activities of abnormal thyroid glands are conveniently studied by the tracer techniques using iodine-131 which is radioactive. This is incorporated almost entirely in thyroid secretion, and can demonstrate the activity or otherwise of thyroid masses. The effect of the radioactivity on the growing cells is made use of in the control of thyroid cancer.

Thyroglobulin is not normally liberated into the blood as such, but is partly digested by a proteolytic enzyme. If it is liberated unchanged it is antigenic, and brings about the collections of lymphocytes and plasma cells often seen in pathological thyroids, and particularly in the lymphadenoid non-secretory goitre called after Hashimoto. The term " goitre " merely means a thyroid mass, and may be hyperplastic, inflammatory, or neoplastic.

The Pituitary and the Pancreas: Diabetes Mellitus

Since the disease diabetes mellitus is successfully controlled by replacement therapy with insulin, it would be natural to regard it as due to insufficient production of insulin through pancreatic disease. The position is however by no means so simple. Clinically, diabetic phenomena are seen in four conditions--

1. Associated with pituitary disorders involving the growth hormone—gigantism and acromegaly. Minor degrees of this association are suggested by the frequency with which diabetic mothers give birth to unusually large babies, sometimes even before they develop clinical diabetes, and by the fact that juvenile diabetics are often tall for their age.

2. Associated with tumours of the adrenal cortex, where glucocorticoid secretion produces low-grade hyperglycaemia resistant to insulin, probably derived from protein breakdown. Conversely, patients with Addison's disease (deficiency of the adrenal cortex) are unusually sensitive to insulin.

3. Elderly obese patients, with low-grade hyperglycaemia, resistant to insulin, rarely associated with ketosis, and treatable by diet.

4. Younger subjects, with rapidly progressive disease, great risk of ketosis, sensitive to insulin, which is a life-saving drug for them.

The untreated patient has difficulty both in utilization and storage of glucose, and therefore has persistent hyperglycaemia, a state of affairs that is shown up more clearly if his uptake is loaded with a test meal of glucose. The renal threshold for sugar is passed, glycosuria results, and a large volume of water is required to excrete

this, for which the patient compensates by drinking. Energy requirements are met by increased utilization of fat, which is increased in the blood, and in its metabolism liberates the toxic aceto-acetic and β-hydroxybutyric acids. The patient thus becomes dehydrated and acidotic; wasting of body protein is added, this being broken down to provide even more unutilizable glucose; the brain is unable to utilize glucose, and death in coma results, often surprisingly quickly.

The untreated disease is never seen nowadays, so that necropsy evidence concerns not the fundamental disease, but the modifications the treated disease imposes on other pathological processes, notably arterial degeneration. The post-mortem examination of the pancreas is in any case often vitiated by autolysis, and while about one-third of cases of diabetes show atrophy of the pancreas (" ribbon pancreas ") this may be the result of replacement therapy; some of the cytological changes described (" hydropic," actually glycogenic, infiltration of the beta-cells of the islets) are due to hyperglycaemia rather than its cause.

Animal experiment has greatly elucidated the position. First came the classical observations linking the pancreas and diabetes, and culminating in the discovery of insulin by Banting and Best in 1922. Formation of insulin in the beta-cells was proved by the specific poisoning of those cells with alloxan. The work of Houssay and Young showed the importance of the pituitary, and particularly that the growth hormone was a cause of persistent hyperglycaemia and that, if this hyperglycaemia was not controlled by insulin, it caused diabetes; even hyperglycaemia itself artificially maintained in a healthy animal could produce diabetes; the persistence of the diabetic state could thus be explained. The curious observation that the insulin requirements of a patient, who had completely lost his islets from carcinoma or pancreatectomy, were much lower than those of a diabetic was illuminated by the demonstration in the alpha-cells of the islets of a substance which broke down glycogen to glucose and so opposed the action of insulin. This would be present in the diabetic but not in the depancreatized man. Many of these points were hinted at by occasional clinical observations, but proof was lacking.

Consequences of the diabetic state—

1. UNCONTROLLED. Apart from the ultimately fatal process of ketosis, the diabetic is unusually prone to infection, which may take on a fulminant course in tissues saturated with sugar. Such were the gangrene of the lung that occurred with pneumonia in a diabetic, and the frequency and severity with which he suffered staphylococcal

infections of the skin. Tuberculosis, urinary infection, and irritant infections of moist skin are unusually common. Excess glycogen and fat are present in the tubules of the kidney—the " terra-cotta kidney."

2. CONTROLLED. The diabetic life is little shortened, though infections remain a risk. The principal difference is in the frequency with which severe atheroma is seen; this has been related to the lipaemia. Gangrene of the feet is therefore commoner in diabetics, and is more likely to be moist and infected. The combination of arterial changes and glycosuria results in the deposition of a glycoprotein in the glomeruli of the kidney, with resultant scarring and hypertension, leading to renal failure (Kimmelstiel-Wilson kidney, intercapillary glomerular sclerosis). Ocular defects are troublesome, opacities in the lens forming one type of cataract, and degenerative changes in the retina which, like the renal changes, may be partly vascular.

Future research has still to uncover the exact primary lesion in the individual human diabetic, more than one being likely. The exact point of action of insulin is still unknown, as is the reason for insulin resistance, and the part, if any, played in human pathology by the substance glucagon formed in the alpha-cells and opposing the action of insulin. There are pointers to a genetic basis for this metabolic disorder, but the position is complicated.

Two rarer conditions associated with diabetes are: (*a*) carcinoma of the pancreas, in which the islets usually escape sufficiently to avoid this sequel, but which may present clinically as diabetes; (*b*) haemochromatosis, in which there is pathological increase in iron absorption from unknown causes; the iron is stored in the liver where it excites cirrhosis, in the pancreas where it causes diabetes, and in the skin where it is associated with increased melanin pigmentation (" bronzed diabetes ").

HYPOGLYCAEMIA. The converse condition, insufficient glucose in the blood, is most frequently seen from excessive insulin dosage in the treatment of diabetes; it may also arise from insulin-secreting tumours of the beta-cells. In either case the result is primarily on the cerebrum which requires steady supplies of glucose. Dizziness, faintness and bizarre mental behaviour not unlike alcoholism precede coma, which is easily and diagnostically reversed by giving glucose, but if overlooked can quickly end in irreversible cerebral failure, since the endurance of suppressed metabolism by the cortex is very short. The attacks occur at times of day when lapse of time since a meal makes the blood-sugar naturally lowest, particularly in the early morning.

The Adrenal Glands

1. CORTEX. A characteristic feature of adrenal secretion is the intensely active output with the minimum of storage; chemical analysis is handicapped by the minute fraction of diurnal output that is available in the excised gland, but has none the less isolated a considerable number of active principles; some doubt still remains which form the natural secretion, and which are the result of chemical extraction processes. The activity of the glands is such that the excision of one is easily compensated by hypertrophy of the other; deficiency will therefore imply bilateral disease.

For ease in discussion, the effects of adrenal principles are classed into three groups: (*a*) those concerned with water and salt metabolism, (*b*) those concerned with carbohydrate formation from protein and (*c*) those concerned with sex. The chemical groupings related to these functions are known, but the details are too complex for inclusion, and many individual substances show more than one effect, though usually one predominates.

(*a*) *Minero-corticoids* (aldosterone; 11-deoxycorticosterone; DOCA is the acetate of this). DOCA is used for implantation in replacement therapy. This is the most immediately important of the hormones, since it acts on the tubular reabsorption of sodium and so prevents the loss of sodium, and hence of water, in the urine. Potassium in the blood is increased when the sodium is lost; this alteration in electrolytes is the cause of death in adrenal insufficiency.

(*b*) *Gluco-corticoids* (11-hydroxy or 11-keto-steroids). These cause increase in blood-sugar by increasing protein breakdown, and enable glycogen formation. This hyperglycaemia is resistant to insulin, and conversely where the hormone is lacking hypoglycaemia sensitive to insulin is found.

(*c*) *Androgens and Oestrogens* (17-keto-steroids). Three-quarters of the body production of these is in the adrenals, and the association of sexual changes in adrenal disease is easily understood. The androgen effects are conspicuous.

As with the thyroid, normal control of the gland is by the adrenocorticotropic hormone of the basophil cells of the pituitary, and similarly the output of this corticotrophin is determined by the amount of adrenal secretion in the blood; where this is adequate or where it is in excess from cortisone therapy, the pituitary stimulus will be less, and may even be inadequate to keep the gland at normal size; stoppage of the therapy will then show up sharply. *Excess* of adrenal secretion may therefore be due to pituitary action (in basophil adenoma, or apparently spontaneous as in Cushing's syndrome),

to neoplasms of the adrenal cortex, the malignant carcinomas being more strongly functional than the adenomas, or may result from therapeutic use of any of the derivatives of cortisone—some more than others; in general, the picture will be a mixed one, in which sodium and water retention, hyperglycaemia, adiposity and virilism will be found. With neoplasms in intra-uterine life, and to a lesser extent with those appearing later, female characters may be masked by male secondary sexual features.

Deficiency (Addison's disease) again may arise from pituitary causes, leading to lack of corticotrophin; from bilateral atrophy of the glands, the reason for which is unknown; from bilateral tuberculosis; or from haemorrhage into the glands, as a complication of some infections (meningococcal septicaemia in children: the Waterhouse-Fridreichsen syndrome) or from adrenal venous thrombosis in hypothermia. It is again a combined affair, but the electrolyte upset dominates all the rest of the picture, and requires immediate treatment if it is not to be fatal. Exhaustion has also been induced by the injudicious use of cortisone and similar drugs medically; the adrenal weakness may be sub-clinical and be shown up suddenly by a surgical operation or similar emergency.

2. MEDULLA. This is destroyed in the Waterhouse-Fridreichsen syndrome, and in tuberculosis of the glands; the resulting hypotension is a natural consequence of the loss of adrenaline and noradrenaline. A rare but dramatic overproduction occurs with a tumour known as a phaeochromocytoma or chromaffinoma; so much hormone is excreted that it can be chemically estimated in the urine. The patients have hypertension, usually paroxysmal at first, often excited by palpation of the tumour, and not lowered by piperoxane; they often sweat excessively and though not invariable, this is a diagnostic sign of value in singling out the one patient who has this tumour from ten thousand other hypertensives.

The Pituitary

1. ADENOHYPOPHYSIS. This is composed of three main types of cell, the *acidophil*, the *basophil* (which are believed to be functionally secretory cells) and the *chromophobe* (which is either an exhausted or an unripe cell). Associated with the acidophil are the growth–diabetogenic hormone (somatotrophin), and the luteinizing and luteotrophic hormones; with the basophil, the adrenotropic, follicle-stimulating, and probably the thyrotropic hormones. The production of these hormones normally depends on the amount of the effective secretion of the target organ reaching the pituitary (except in the case of the growth hormone), a feedback mechanism stopping

the production of the primary trophin. The effect of these hormones has been discussed in relation to their target organs; excess will arise from functional secretory benign tumours, deficiency from vascular disturbance in the gland; possibly from neurogenic influences via the hypothalamus; and from tumours of the non-secretory chromophobe cells displacing the others.

The growth hormone has not been discussed yet. In excess, it gives rise to continued excessive growth at the cartilaginous epiphyseal plates until the time of their union (gigantism); after this the bony growth is in thickness rather than length, leading to the spatulate hands, prognathism and heavy brows of acromegaly. Protein uptake is increased in the whole body as well as in the bones. Lack of the hormone results in dwarfing. The hyperglycaemic effect of this hormone has been alluded to (p. 201) and diabetes is common in acromegaly, as is some gonadal disturbance; the pituitary is a small organ with many functions packed into it and clinical disturbances are likely therefore to be mixed.

The two important causes of pituitary disturbance are neoplasms arising in the gland itself or near it (suprasellar cysts of Rathke's pouch), and vascular damage, notably that occasioned by severe post-partum haemorrhage on a pituitary physiologically enlarged by pregnancy; partial or complete necrosis of the gland may follow.

2. NEUROHYPOPHYSIS. This is very closely linked with the hypothalamus, both by the pituitary-portal blood-vessels, and by neurosecretion; the hormones of the posterior lobe can be demonstrated in the hypothalamic nuclei and the nerves issuing therefrom. Further experimental work in this minute area is likely to involve both structures. Of the two known hormones, oxytocin is more of a drug extractable from the hypophysis than a hormone; but the antidiuretic principle (which has also a pressor effect in experiment) acts on the tubular reabsorption of water in the kidney in proportion to the osmotic pressure of the blood in the carotid chemoreceptors. Tumours, injuries and the deposition of cholesterides (Hand–Schuller–Christian disease, xanthomatosis) in the area may therefore result in polyuria.

The Sex Glands

In addition to their primary function of forming gametes, these glands also control the accessory organs of reproduction, and non-development or ablation of the sex glands will be associated with atrophy or hypoplasia thereof. In both sexes, there is dependence on the adenohypophysis in these functions, and additional sources

of some of the hormones or closely related chemicals are present in the adrenals. The cells responsible for the secretion are the interstitial cells of Leydig in the testis, and the cells of the Graafian follicle (other than the ovum) in its two phases of follicular and luteal activity in the female.

MALE. Androgen secretion in the form of testosterone (a 17-keto-steroid) is responsible for the development of the male sexual characters but does not control spermatogenesis; this may be directly under hypophyseal control. There may be oestrogen secretion by the Sertoli cells, which are mainly concerned with the nutrition of the developing sperm.

FEMALE. Oestrogen secretion is the work of the follicular cells before luteinization, and is responsible for the secondary female characters, and for the proliferation of the endometrium in the first part of the menstrual cycle. After luteinization, the hormone secreted is progesterone, concerned with the secretory phase of the menstrual cycle, and implantation of the fertilized ovum; cessation of this secretion results in menstruation, withdrawal of both oestrogen and progestin having this effect. The appearance of secretory changes in the endometrium is regarded as evidence that ovulation has occurred and the thecal cells are becoming luteinized.

The effects of excess secretion will be seen with tumours arising from these secretory cells, the oestrogen-secreting tumours of the ovary ("granulosa-cell tumours") being the commonest, and occasionally giving rise to puberty in very young girls or continuing menstruation in late life.

Deficiencies are more commonly observed, sometimes due to gonadal disease, sometimes hypophyseal and then usually associated with evidence of other hypophyseal dysfunction. If they occur before development is complete at puberty, the result is hypoplasia or faulty development of the organs; if after puberty, though there may be some modification in secondary sexual characters, the results are usually physiological dysfunction. Weak stimuli in early embryonic development may produce apparent intersexual forms, the secondary characters of which may be modified by treatment or by other endocrine influences, but which are rarely rendered completely sexually normal. Difficulty in determining the true genetic sex from malformed organs may be eased by observation of the sex of the nucleated cells—from cheek mucosa, or polymorph leucocytes (p. 265).

Although the considerable quantity of androgen which can be demonstrated chemically to be secreted by the adrenal glands is responsible for the virilizing effect of adrenal tumours, it does not

compensate for the loss of the much smaller quantity of androgen produced by the testis, in patients with non-functional testes.

Pigmentation

Apart from local and unimportant deposits of carbon, tattoo pigments, and iron around metallic foreign bodies, the colours seen in pathology are endogenous, and derived from four main sources. The most important is blood, both in its unaltered state and in the process of breakdown into haemosiderin and bilirubin (haematoidin); melanin and the lipochromes are less important but common enough. To guess at the origin of brown pigments is likely to lead to errors; melanin should be proved by Fontana's silver reaction, haemosiderin by acid ferrocyanide and lipochrome by nile blue or acid-fast techniques. In practice, if iron is excluded, the location of the pigment and the kind of case will usually decide between the others.

1. FRESH BLOOD. At necropsy, blood is oxidized on cut surfaces and quickly covers organs with an even red colour; therefore never give an opinion except on a fresh-cut surface. Thus the pink colour of carboxyhaemoglobin is easily overlooked once the body is opened. The position of the body after death (usually on the back, in hospital) as well as the distribution of blood at the time of death, determines the degree of congestion of organs and this should be allowed for; the distribution of hypostatic congestion may be of medico-legal importance. The basic colour of organs is much modified by the amount of blood they contain; in severe anaemias, the organs may be very pale.

2. THE BREAKDOWN PRODUCTS OF BLOOD are conspicuously different in their solubility; haematoidin is soluble and will diffuse away from sites of haemorrhage within a few weeks, during which various shades of yellow and green are seen; haemosiderin is insoluble and usually intra-cellular, and therefore is more permanent; when it is present in excess the organs are rusty red-brown. The green staining seen in the abdominal cavity in the bodies that have been dead for two days is ferrous sulphide, due to the breakdown of blood by putrefactive organisms derived from the gut; when this is unusually conspicuous in a recently dead body it should suggest excess iron storage in the liver.

JAUNDICE occurs when there is general staining of the tissues by bilirubin. This may be the result of excess haemolysis (haemolytic anaemias, breakdown of large haemorrhagic pulmonary infarcts) leading to more bilirubin than the liver can excrete; it may be the result of damage to the liver cells (toxic or hepatic jaundice)

preventing them from excreting the normal amount of bilirubin; these causes may be combined—haemolytic anaemia providing both the excess bilirubin and anaemic dysfunction of hepatic cells, congestive cardiac failure and "nutmeg" liver combined with pulmonary infarction. The third common cause of jaundice clinically is obstruction to the common bile duct; this leads to a much deeper jaundice, and to the absence of bile salts and bile pigments from the stools.

3. MELANIN is formed by melanoblasts in the skin, uveal tract of the eye, and occasionally locally elsewhere, and by some neurones (substantia nigra), from tyrosine by the action of an enzyme tyrosinase. It is responsible for the natural colour of the iris, freckles, and the skin, and is much increased following irradiation with excess sunlight or X-rays, in arsenic poisoning, and in Addison's disease of the adrenals, the reason being obscure. It is absent in albinos, who have no tyrosinase, in the conspicuous skin disease melano-leucoderma or vitiligo where the cells are absent in the pale patches, and in scars, though there is often at least an apparent increase around them.

Melanin is also present in many but not all tumours of melanoblasts, the amount being great enough to darken the urine in patients with massive secondary deposits from malignant tumours of this type. All black tumours are not melanomas; dirt, old haemorrhage, and stored iron in some skin tumours are misleading.

4. LIPOCHROMES are pale brownish pigments seen as fine granules near the nuclei of cells; their purpose is obscure. When an organ shrinks, this pigment becomes concentrated and atrophic organs are dark brown from this; the pigment may also be observed in phagocytes following removal of cells. Other intra-cellular pigments of the cytochrome and porphyrin groups are at present unstudied, or related to rare disorders only.

Warning should perhaps be given of the dark-brown pigment that is precipitated by unneutralized formalin in bloody organs, which can be very puzzling in sections.

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CHAPTER 7

DISORDERS OF GROWTH

THE cellular function of growth which has been so obvious in the child and young adult gradually subsides as the adult state is reached until in the interior of the body it is equated to the maintenance of the adult size. On external surfaces the continuation of growth of the skin and hair at a rapid rate is obvious; deduction from experimental animal observation and from mitosis counts in the human suggests that the lining of the alimentary tract is in the process of daily renewal. Further, the natural continuous turnover of bone has been known since the day of John Hunter. There are a few organs where cellular replacement is known not to occur—the neurones, and probably cartilage, in particular. With these exceptions it cannot be proved not to occur and there is circumstantial evidence that it does occur continuously and that in fact the continuous replacement of cells is part of their health.

This function is normally strictly controlled by the requirements of the part, though we do not know much about the exact way in which this control is exercised. We do, however, see in pathology two conditions in which growth is excessive; these are respectively referred to as *hyperplasia* and *neoplasia.*

Hyperplasia

In this process the purpose of the growth, from the point of view of the colony as a whole, is easily understood. The part affected is always the whole of an organ, or a segment of an organ which has a functional significance as a whole. The overgrowth is of healthy tissue resembling the normal in structure and function, except in so far as secondary changes from shortage of blood supply or other deterioration may occur. The overgrowth ceases when the stimulus ceases, and the overgrown tissue may revert to the normal, though usually incompletely.

The points may be illustrated by examples. A few cells can actually increase their size in order to increase their output. This overgrowth, referred to as *hypertrophy* rather than hyperplasia, though the usage is not strictly observed, implies the increase of

size of cells without any increase in number. The best example is the overgrowth of muscle fibres with added load, whether this is hard work affecting the voluntary muscles, or the load of working against a pathological obstruction as in the cardiac muscle of the left atrium in mitral stenosis, or the smooth muscle of the colon pushing the contents through a constricting carcinoma. Examples of hyperplasia are the overgrowth of one kidney following the excision of the other, the overgrowth of the parathyroid glands when there is phosphate retention, the thickening of the skin in the functional segment that takes the friction of hand tools or the pressure of ill-fitting boots. The function of the overgrown tissue is clear: the appearance both macroscopic and microscopic is that of the normal tissue; the physiological mechanisms are identical; all four parathyroids take part more or less equally. In the last example the only part of the skin involved is that exposed to pressure, and if pressure is relieved the overgrowth returns to normal.

Neoplasia

This is contrasted at every point with the foregoing. (Plate 13.) The new tissue does not fulfil any obvious function in the economy of the body as a whole. The part affected is at first always local (though it may be multiple at the start, and may spread to involve the whole organ eventually) and the local area has no functional delimitation. The new tissue may resemble the normal, but it more often differs in detail and may be so unlike the normal that it is difficult to relate the tissue and the neoplasm. The stimulus for some neoplasms is known, but the character of the induced growth is such that even when the stimulus is abolished the growth continues.

It is sometimes stated that the neoplasms do not obey any of the laws of normal tissue, and the definition " autonomous new growth " is used. This is demonstrably incorrect: many neoplasms are clearly under the influence of the hormones of the patient, and all are subject to the requirements of nutrition, though their metabolism is not identical with that of the normal. Although somewhat long, the definition given by Willis (1949) is of value in separating the class of neoplasms on the one hand from the hyperplasias and the congenital malformations on the other. It runs as follows—

> A neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissue, and persists in the same excessive manner after the cessation of the stimuli which evoked the change.

The popular view that there is a single disease " cancer " for which there is a single cause and for which there may be a single

cure is true only in the very broadest sense. It is much better to compare neoplasia as a whole to inflammation as a whole; both are processes derived from the normal processes of the body, excited by a large number of quite unrelated causes. Inflammation differs from neoplasia in that the effects are beneficial to the organism as a whole, while those of neoplasia are at the best indifferent and at the worst destroy life. Inflammation has evolutionary value; neoplasia so much the reverse that it would be eliminated by evolution if it did not mainly occur when reproductive life is over. But both are cellular reactions to stimuli, many of which are well known, many unknown; the effects of inflammation and neoplasia on the cells which take part have no connexion with the possible results on the organism as a whole. Man has survived because the cellular process of inflammation has a value for the organism; it is teleological thinking to suggest that the inflammatory reactions in the cell result because the cell intends that organism to survive. Similarly the disadvantages from neoplastic growth are irrelevant to the consideration of why the cell reacts this way to some stimuli, and by inflammation to other stimuli.

Classification of Neoplasms

The form taken by neoplastic growth falls into one of two patterns; in one, *benign* growth, the new tissue increases in bulk, and makes room for itself by displacing other tissues or projecting into any available cavities; it remains of the histological type of the parent tissue; the ill-effects produced result from the complications of bulk, or in the case of endocrine glands from the formation of excessive secretion.

In the second type, *malignant* growth, in addition to increase in bulk, the tumour cells have the power of invasion between the surrounding cells, and further, can migrate along natural channels or otherwise to new situations where they may grow; they may continue their invasion and spread from these new foci, so that before the patient dies many hundreds of *secondary* growths may be present in his body; death may result from the development of these rather than from the primary focus itself.

To this change of location the name *metastasis* is given, the term being used both for the process and for an individual mass of secondary growth that has arisen in this way. As generally used, it does not include direct spread from the edge of the primary tumour, even when separated by a short strip of normal tissue. The routes of spread include natural lined channels—the lymphatics; the blood-stream; possibly bronchi and other ducts, the best proven example

being metastasis of carcinoma of the body of the uterus along the Fallopian tube to the ovary; the cerebro-spinal spaces; and the pleural, peritoneal, and pericardial sacs. Which route is chosen by a given tumour is largely a question of access; there is a general tendency for carcinoma to prefer the lymphatics, sarcoma the blood-stream, but almost any malignant tumour may on occasion spread by any or all of the above routes which its cells can reach. Trans-plantation may occasionally result from surgical instruments; metastases in abdominal operation scars from gastric or colonic cancers develop this way.

This capacity for multiplying and spreading is what gives the malignant tumour its serious prognosis; even single cells left behind after a surgical operation may keep the process going. At the same time it must be emphasized that these are pathological terms; benign tumours may kill if their situation (e.g. intra-cranial) or their excessive secretion (e.g. islet-cell tumours of the pancreas) is sufficient, and slowly growing malignant tumours in unimportant sites (some skin and prostatic growths) may not shorten life at all.

When the disease has run its course fully the neoplastic process will always fall clearly into one or other pattern. When the early stages alone are to be considered in the medical care of a patient, the decision may not be clear-cut, since at the time when it is desirable to treat the patient, the malignant tumour should show no metastasis and little or no invasion; the decision of its nature then turns on histological evidence. To the two points of invasion and metastasis, which are absolute evidence of malignant behaviour, is added a third, purely histological point, *atypicality*, which requires much more experience and judgement and about which there may be argument. Atypicality, as well as being the most difficult, is also the earliest and most delicate indication of a malignant process; by this term is meant that the cell-type varies from the cell-type characteristic of the normal organ. The degree of variation is very wide; at the one end come cells so like the normal that their neoplastic character is uncertain, and benign tumours tend to this kind; at the other end come cells so unlike the parent tissue that it may be quite impossible to relate them without clinical evidence. Broadly speaking the malignancy of the growth increases with the degree of atypicality but there are two points here—one is that the histological sample is only a small one of a growth, the other that it is not the average of the whole growth that determines the outcome, but the worst part, which may only be a few cells in size.

There are then these two fundamental groups of neoplasms, the benign and the malignant; it is easiest to make the definition strict,

that the possession of any one of the three points, atypicality, invasion or metastasis, implies that you are dealing with a malignant tumour. A benign tumour will never show any one of these, unless it is changing its nature; this may occur occasionally though it is common only in a few special cases, notably the colonic and vesical papillomas. The converse change, a malignant tumour losing its character, is nearly unknown, though from time to time such tumours die out altogether. It is clear that there will be all clinical variations in malignancy: speed of growth, invasiveness, metastasis, and the mechanical effect of the presence of the tumour lead to a very great scatter of importance in this subject. In particular note that any one characteristic of malignancy is enough to class the tumour as a malignant one; it is not necessary to demonstrate all three; a tumour which does not metastasize is not necessarily benign. Recurrence is not necessarily evidence of malignancy; it may take place if a benign tumour is not completely removed—an outlying lobule of a lobulated mass is easily overlooked. It is better in the definition to ignore such points as the fate of the patient and the rapidity or slowness of growth, since these are not necessarily directly related to the kind of growth and in practice prove unreliable criteria.

Classification

After the principal primary division of tumours into the groups benign and malignant, they are subdivided according to the tissue in which they take origin, and named as in the Table on page 217. This is based partly on the naked-eye appearance, but is always in practice confirmed by the microscopic study of the cellular structure of the growth.

If further classification of carcinomas is required, it can be done by describing the cells of which they are composed, e.g. squamous and horny, tubular columnar-celled; the term "adeno-carcinoma" is in common use for a carcinoma retaining glandular architecture, but it is not a halfway stage between benign and malignant.

In addition, the tumours of the ovary, and the groups marked with an asterisk on page 217, have been subject to intensive study by specialists and many special categories and names have been delimited; often the tumours are rare or very rare. Some of the detail will be given below but a complete account of these complications is beyond the scope of the book. Over 99 per cent of the neoplasms met with in ordinary medical life can be covered by the categories given above.

The classification has the advantage of combining a good deal of

the natural history of the growth with the macroscopic and microscopic appearances. But it can never be too strongly emphasized that the natural history of a particular growth in a patient is an individual affair and that prediction, except on the most general terms, in the individual is unsafe, even when the statistical behaviour of the group is well known. Our knowledge of the natural history of even the most common growths is very far from complete, and study of the benign group in particular has hardly begun.

Benign		Malignant
Arising from surfaces		
Squamous epithelium	Papilloma	Carcinoma (the term "epithelioma" is sometimes used; as the meaning is not the same in all parts of the world, and as it is an unnecessary additional term, it is not used here).
Transitional „	„	
Glandular epithelium (whether on surface or in a solid gland)	Adenoma	Carcinoma
Arising from supporting structures		
Bone	Osteoma*	Osteosarcoma*
Cartilage	Chondroma	Chondrosarcoma
Fibrous Tissue	Fibroma	Fibrosarcoma
Fat	Lipoma	Liposarcoma
Blood-vessel	Angioma	Angiosarcoma
Glia	Glioma*	Gliosarcoma*
Smooth muscle	Leio-myoma	Leiomyosarcoma
Special cases		
Arising from—		
Melanin-producing cells	Benign Melanoma	Malignant melanoma
Reticulo-endothelial tissues*		
Primitive cells, of embryonic tissue		Nephro-, neuro-, medullo-blastoma
Notochord remnants		Chordoma
Arising from germ cells, capable of developing into many kinds of tissue		
	Teratoma	Malignant teratoma

Note: The strict Greek plural for these terms is -ata (adenomata, sarcomata) but the colloquial English plural -s (adenomas, sarcomas) is usually acceptable.

The medical problem of deciding from a small microscopical sample the category to which the neoplasm belongs in a patient who is still living is quite different from that of classifying the processes when they can be studied whole, and is dealt with separately in the section on biopsy (p. 255).

Growth and Nutrition in Neoplasms

ORIGIN. It can be shown in some groups of neoplasms that origin is from a considerable area of tissue and not from a single cell. This multifocal origin may be obscured in most clinical examples by the confluence of the separate foci, but the more it is looked for the more regularly it is found. This origin has both a theoretical and a practical import; it is improbable that a change in the skin such as that seen in Plate 14 could have arisen from a genetic or similar change in a single cell; and if recurrence after operation is to be avoided it is clear that the area excised must include the whole field of origin of the tumour, a much wider area than appears on the surface to be involved.

NUTRITION AND GROWTH (Plate 15). From this area of origin, the change in the cells of the tumour will cause it to proliferate and grow in bulk. The growth will at first take the easiest directions—towards the surface and into the lumen where there are such, or radially if the growth is in soft tissue such as lung or liver. This is without any regard to the tissue of origin, or whether the tumour is primary or secondary.

As the tumour grows it will not have an organized vascular supply like that of a healthy organ, but will have to obtain what it can from the capillaries of the part. This early results in the centre of the growth becoming less well nourished, and in malignant growths with their more rapid cell-division frank necrosis is usual in masses of any size. Some slow and functionless benign growths may remain healthy although very much larger, apart from the apparent growth that is really accumulation of fluid in cystic tumours. This necrosis is well seen in the centre of large secondary growths in the liver, and in the middle of the plaque-like growths that are found on surfaces.

To this expansive growth in bulk the malignant neoplasm adds its invasive powers, and grows by pushing between cells, where the benign will only displace tissues; benign tumours may extend along the interstices of bone. As a consequence, the edge of a malignant tumour is never smoothly rounded, unless its expansive growth is greater than its invasive; the border is ill-defined, nodular, irregular, and becomes attached to neighbouring structures. Particular

consequences result when the part invaded is the muscle of a hollow viscus. A benign growth may be sessile, but is often pulled off the underlying tissue by muscular action and becomes polypoid, with a thin stalk containing the blood supply; this narrow pedicle may be twisted and the tumour cure itself by infarction. The invasive tendency of a malignant tumour leads to attachment to the muscle; pedunculation is less common, and inversion of the muscle coat (intussusception of the gut) may occur. Other consequences of invasion are the interference with nerve-trunks, with severe pain; until this occurs cancer is a painless disease; the slow growth is in contrast with the rapid painful swelling of an inflammation.

An important observation in connexion with these activities of malignant cells has been made by Ambrose and Abercrombie. Normal cells in tissue culture cease moving when their surfaces come in contact; this does not happen when a malignant cell makes contact with other cells. This may mark a significant difference in the character of the surface of the malignant cell which is related to its behaviour in the body.

Cause of Death in Cancer

The cause of death from malignant disease is not always clear, but the mere presence of neoplastic masses in the body is only a small part of it; they may reach a considerable size in places where they do not affect important structures. Much is mechanical; interference with gastric, bronchial, or other transport; rupture of a viscus where the normal wall is replaced by growth; ulceration of the neoplastic epithelium exposing a blood-vessel and leading to haemorrhage. These may be due to primary or secondary growth. Bone secondaries as well as interfering with blood formation may render the patient bed-ridden by paraplegia or pathological fracture, and urinary or bronchial infection prove fatal. Discomfort from large masses and pain from neural involvement combine with the knowledge of the nature of the illness. Absorption from necrotic masses may lead to fever and " toxic " symptoms, but most of the " cachexia " of advanced malignant disease can be explained more simply as above. There are however well-established examples of a " toxic " effect (e.g. carcinomatous neuropathy, p. 233).

Common Illustrative Examples of Neoplastic Growth

Benign Growths of Epithelium

The simplest example is the common wart. The stimulus to proliferation here is the colonization of the skin cells by a virus; the

infectivity of these warts is frequently demonstrable. Multiplication of the basal cells in excess of that required for normal loss results in the appearance of thickening and the formation of folds of the proliferating epidermis and keratin, which gives the fine papillary processes with fissures between. Infection of these crevices and bleeding from injury are commonly seen and the imperfect keratinization of the neoplasm allows this. In time the virus dies out and the tumour disappears in the ordinary course of the growth of the skin. Similar papillomas are known which do not have any virus; they may follow tar handling, the application of irradiation, or may come spontaneously. In older people, change to malignant growth may occur. The *corn* is a local hyperplasia following pressure or friction; it affects the area directly related ("functional segment") and resists the damage the friction would otherwise do; when the pressure is relieved the overgrowth disappears.

Papillomata occur from other squamous surfaces; from the ducts of the breast (p. 222); from the bladder, a very important one, which forms a mass of delicate fronds which bleed easily; it is commonly multiple and often, apparently after a long benign course, changes to carcinoma.

Projecting growths of other kinds are often clinically called papillomata—pedunculated fibrous tumours, melanomas, even inflammatory masses. The correct classification depends on their histology.

Benign Growths from Mucous Surfaces

Two of the commonest tumours found in the human body are the benign adenomata of the uterus, which are typically polyps and known as *endometrial and cervical uterine polyps*. In each, a typical piece of the mucosa becomes enlarged and grows at first into the uterine cavity, then may be thrust out slowly by the uterine muscle till it presents at the os. Strangling of the pedicle leads to congestion or necrosis and the whole may be sloughed. Another common example is in the colon and especially the rectum, where similar long-stalked tufts of rectal mucosa are found.

It will be noticed that the term " polyp " does not imply anything more than a stalked object; polyps may be inflammatory, consisting of granulation tissue or inflamed mucosa (e.g. the aural and nasal polyp); benign tumours and malignant tumours both primary and secondary on occasions show this form of growth. It is a descriptive term, not a pathological classification.

Benign Growths of Glands

These form rounded encapsulated masses of small to moderate size which displace the surrounding glandular tissue and shell-out of this capsule when dissected skilfully by the surgeon. Many examples are known; they cause trouble in three ways, which make convenient headings for the groups.

1. Those of functional secretory endocrine tissues—a very important group indeed in which minute tumours may prove fatal by secretion of the hormone. Tumours of this sort arise from both the acidophil and the basophil cells of the adenohypophysis, from the islets of the pancreas, and the parathyroids. In each case symptoms result from excessive hormone production; the tumours are so typical that they not only resemble very closely the appropriate cells histologically, but the chemical secretion is also exact, and the consequences can be deduced from the effects of the normal hormone.

2. Those in which there is no very marked secretory effect, but the masses cause trouble by pressure or interference with passages. Such are the adenomas arising from the chromophobe cells of the adenohypophysis, which not only compress the other cells but also the optic tracts above, and other related structures; a large tumour of the acidophil cells may do the same, in addition to its endocrine effects; the tumours of the basophil cells are never large enough to do so. The majority of adenomas of the thyroid are in this group, since although they elaborate thyroid colloid their presence is not associated with thyrotoxicosis as a rule. The border between hyperplasia and neoplasia is indistinct in this group, and cases can be found with one, two, three . . . tumours until a case is found with so many that nodular hyperplasia of the whole gland seems a better title. The thyroid masses may be unsightly; more important, they may compress the trachea, in particular those in which haemorrhage has occurred or which slip down into the thoracic inlet.

An even more important and common member of this group is the enlargement of the prostate in elderly men. The enlarged masses represent most of the lateral lobes of the prostate, and are multiple; they are related to the endocrine state of the patient, more especially the internal secretions of the testis, and do not form in patients whose testes are atrophied or absent. Although the condition causes clinical symptoms by its mass, as benign tumours do, it comes nearer in pathological classification to a hyperplasia, and is best described by the non-committal term " senile enlargement of the prostate." The masses consist of typical prostatic gland acini with

the smooth muscle, which is also found between the normal prostatic acini, and which may make up the whole of a lobule of the tumour; the alternative name " myoadenomatosis " of the prostate acknowledges this.

3. In the third group come masses which are of no importance in themselves, but are unsightly, otherwise cosmetically undesirable, or sufficiently like malignant tumours to worry their lay owners and sometimes the doctors as well; for these reasons they are excised. Some thyroid adenomas, tumours of the sweat and Bartholin's glands, salivary gland tumours, breast tumours come into this group. The last two merit special mention.

THE SALIVARY GLAND TUMOURS have for long been known as " mixed " because the mucus they secrete becomes mixed up with the stroma and somewhat resembles cartilage, a resemblance close enough to lead to ossification now and then. It was thought for a while that this implied origin from two sorts of tissue, and the tumours were named accordingly, but they probably derive entirely from the salivary epithelium. They are slowly growing tumours, found in young people, mainly in the parotid but occasionally in other salivary glands, including those of the palate; they are prone to recur, maybe more than once, but displace rather than invade and it is unusual for them to metastasize; the more cellular and especially the palatal examples are just that little bit worse than the ordinary adenoma to deserve a special name.

IN THE BREAST, the adenoma is accompanied by a stromal overgrowth that makes a combined tumour known as a *fibro-adenoma*, a rounded encapsulated mobile elastic mass found in women of all ages from puberty and occasionally in men. Although in elderly women a malignant change to sarcoma in the stroma is known, the tumours are typically benign.

From the epithelium lining the mammary ducts grows the *duct papilloma*, an irregular branching mass that causes symptoms partly by bleeding, partly by blocking the drainage of secretion from even a non-lactating breast. The papilloma does this before it becomes palpable itself, giving rise to mammary retention cysts; these may become infected by organisms of low virulence and form chronic abscesses. The duct papilloma may become malignant, but more important is the nodularity it and its cysts produce, which may imitate or conceal a carcinoma.

Malignant Epithelial Tumours—Carcinoma

The greatest number of what the layman calls " cancers " fall into this group, and it is therefore of outstanding importance. Very

great variety in appearance and behaviour is found, and this book can only touch on the subject.

In general, carcinomas form hard irregular masses or ulcerated plaques if on a surface, often granular on section, and centrally necrotic; these are the result of a considerable fibrosis excited by the presence of the tumour cells, dividing them into small groups, and with the invading cells binding the mass to adjacent tissue. Although a number of inflammatory cells are seen in many examples, no effective limitation of the tumour results. Metastasis is mainly by lymphatic channels in the first place, but trans-pleural or peritoneal routes are regular when opportunity offers, and blood-stream metastasis is regular in most carcinomas if the patient survives long enough, while a few examples favour this route either early (lung cancer) or nearly exclusively (liver, kidney). Blood-borne secondaries go to the liver from growths in the portal circulation, to the lung from the systemic, but these tumour emboli can force their way through the capillaries to the arterial circulation and be scattered in many organs. With some tumours, this blood-stream spread results in a peculiar selective colonization (e.g. lung primaries send their blood-stream metastases to the brain and adrenal), and no tumours seed themselves completely impartially—subcutis and voluntary muscle are spared; clearly the tumour cells find some soils more receptive than others, and a very large number must remain latent or die. It is possible that in fact from the very earliest stages of the growth cancer cells are present in the blood but do not succeed in establishing themselves as secondaries with any frequency; and it is certain that even gentle manipulation of a growth increases the number of malignant cells spread from it.

The outlook for the individual patient with cancer is at least as much determined by the extent of spread at the time of treatment as by histological characters of the growth, though both this, judged by the degree of atypicality, and the natural speed of the individual growth, judged from the history, must be taken into account. The aim of early diagnosis is to anticipate the critical moment of the onset of metastasis; this may be quite a sudden affair, a single tumour reaching a vein one day, and fifty blood-stream secondaries being present the next. No delay between diagnosis and treatment is tolerable.

The description in detail of the members of this group of tumours is impossible in the space available, and must be studied in larger books; that by Willis is the fullest and most up-to-date; the six-volume work under production by Butterworths is likely to be authoritative on the whole subject of cancer and one volume is

devoted to the pathology of tumours, but says little about benign tumours.

Here each important class of carcinomas is used to illustrate some general principles in the study of the subject, as follows—

Squamous-celled carcinoma:
- Differentiation and grading.
- Pre-carcinomatous states.

Glandular epithelial carcinoma:

Solid glands—breast and prostate.
- Hormone dependency.
- Reaction to tumours.
- Delayed metastasis.

Glandular surfaces—stomach and lung:
- Investigation of the causes of a common growth.
- Changes in incidence of growths.
- Individual peculiarities of growths.

Carcinoma Arising in Squamous Surfaces

These are found on the skin, and two very important examples on internal surfaces—the cervix uteri, and the oesophagus and buccopharyngeal mucosa in general. The form taken is characteristically a raised nodular plaque with an everted edge, but any form from warty papillae to flat plaques may be seen. Ulceration and haemorrhage are usual, invasion early with spread to lymphatic glands. On the whole, direct spread, ulceration and haemorrhage lead to death before there is very marked blood-stream spread, e.g. the interruption of the ureters by direct lateral spread from cervical uterine cancer, and the starvation or perforation into the lung or mediastinum that occurs in oesophageal growths. Apart from the uterine tumour, there is a 3:1 male sex preponderance in this kind of growth.

The degree of histological differentiation varies greatly, even in one clinical example and its secondaries. The majority make recognizable keratin in the form of concentric lamellae which are known as cell-nests or horny pearls; they can be recognized even in the necrotic centres of growths, e.g. in secondary cervical glands that have undergone necrosis and produce material that resembles pus. This variation in differentiation is made use of in *Broder's grading* which attempts to classify four grades of malignancy, (1) being the most differentiated, (4) the completely undifferentiated; but the variation in an individual tumour and the small sample possible for the histologist make it difficult to divide the two middle classes, and it is usually enough to state that the tumour is particularly well- or particularly ill-differentiated (or *anaplastic*).

On the whole malignancy runs parallel with lack of differentiation but there is considerable individual variation. The tumours arising in scars are slow-growing, particularly those in varicose ulcers and osteomyelitis scars, those of the buccal and oesophageal mucosa dangerous. The group as a whole is one of the most strongly radiosensitive.

A sub-group of the skin cancers is common enough to deserve separate mention, the *basal-cell carcinoma or rodent ulcer*. Although deeply and dangerously invasive, the rate of growth is slow and metastasis quite exceptional. The tumours are found on the face, especially around the eye, and on the scalp and trunk. They form plaques with rolled edges, sometimes of considerable size, sometimes small and fissured. Histologically the cells resemble basal cells of the epidermis, and differentiation to keratin is not found. The origin in continuity from the basal cells of skin or appendages is easy to demonstrate; some of those on the scalp develop mucoid material and large rounded masses of cells that are called turban tumours. They are radiosensitive.

Intermediate members between basal and squamous cell tumours are known, as are pre-invasive skin carcinomas, known to dermatologists by the names of their observers (Bowen's disease, Quezrat's erythroplasia, etc.). An interesting but uncertain squamous-cell growth with the histological picture of a well-differentiated carcinoma and a strong tendency to spontaneous healing has been recently described under the name kerato-acanthoma. The importance of this observation is its bearing on the histological feature of invasion which is regarded as evidence of malignancy. This tumour shows invasion; either this criterion of malignancy is unsound, and the typical cellular picture is a better guide, or else it has to be admitted that some malignant tumours can heal spontaneously. This is not a common observation, but further suspicion of the view that all malignant growths progress inevitably to death is raised by the recent diagnoses of cancerous changes in the epithelium of the cervix uteri on the cells exfoliated into the vaginal fluid. No invasion has occurred, and the condition is described as " carcinoma *in situ* " and treated as very early malignant growth. A small number of patients who were not so treated for various reasons were seen later to have no advanced malignant growth; this again suggests that early cancers may disappear in a stage of very early growth. This must not be taken as giving any reasonable probability that an established malignant growth will regress, though again rare examples of this have been reported from time to time.

PRE-CARCINOMATOUS STATES. Observations of the above kind have

provided clinical support for the experimental observation that there are preceding changes, some visible, others not, in an epithelium that is destined to develop invasive cancer. Basing a histological diagnosis on atypicality rather than invasion has led to the description of " pre-invasive " carcinoma or " carcinoma *in situ*," but even before this change was recognized the epithelial condition known as *leukoplakia* was clinically associated with carcinoma. In this, the epithelium is hyperplastic and keratinized and so whiter than normal, often cracked and with inflammatory cells in the dermis. The association with carcinoma is best seen in the vulva, where there is a high probability of cancer, and on the tongue. Other conditions in which the epithelium is unstable are scars of chronic inflammation, in particular those of irradiation, and sometimes those of burns, osteomyelitis, and varicose ulcers. In this whole group the field origin of cancer is very well shown; the entire affected area is potentially dangerous, though frank malignant growths have occurred at only one part of it.

Malignant Growths of Glands—Solid Glands

The principal member of this group is the very common carcinoma of the breast, which ranks about third in overall frequency and moves up to first place in women. Other sites of importance are the prostate in the male, possibly an equally common growth but one that as will be seen is of less clinical importance, the pancreas and thyroid.

CARCINOMA OF THE BREAST. The most interesting point about this growth (which is a typical member of the class Carcinoma in most respects) is the frequency with which it shows some relation to the normal hormonal control of the breast. This has been used in treatment—ovariectomy was tried fifty years ago by Beatson in Glasgow, and more extensive ablation of the endocrine stimuli is now under trial for widespread metastases, and sometimes holding the growth in check. It is rather as a possible approach to treatment in the future than as a present success that this must be considered; it underlines the fact that malignant growths do not exist as entirely independent entities, but are related to the body in which they grow. The point is illustrated in reverse by the fulminating growth of mammary carcinoma in a pregnant woman (mastitis carcinomatosa, because it is clinically like an inflammation). The growth is occasionally found in the male, and most often when there are feminizing changes; it has so occurred following the use of stilboestrol to treat males for carcinoma of the prostate. Frequency studies show that the physiological use of the breast lessens the likelihood of developing carcinoma.

Much work has been done in the aetiology of this carcinoma in the mouse (p. 254), where it is possibly hereditary, possibly transmitted from mother to daughter in the milk, and can be produced by oestrogen injection. No definite cause is known in the human, and different results have been put forward by investigators in Holland, Norway and Britain on the hereditary tendency to it.

In the later stages of the reproductive life uneven hormonal control of the breast leads to irregular epithelial growth in the organ, with duct blockage, cyst development and sometimes secondary inflammation; this is known under a variety of names—fibroadenosis, chronic cystic mastitis, chronic interstitial mastitis—which emphasize too much the inflammatory part. It is sometimes thought to be pre-carcinomatous, a point that is hard to prove because of its frequency in women near the age where carcinoma begins; it is likely enough that where there is one form of epithelial irregular growth another form might be found; proof that the risk of cancer is much greater in cystic mastitis is not complete.

Paget described in 1874 a disease of the nipple which was followed within two years by mammary carcinoma. Histology of this condition shows a pre-invasive stage of carcinoma in the nipple and usually in the ducts of the breast, with sometimes frank invasive growth. It is not a pre-carcinomatous condition because it is carcinoma already, albeit in an extensive field of pre-invasive growth and not a local mass. It must be differentiated from the other two ways in which carcinoma of the breast involves the skin—direct invasion, and permeation of the deep dermal lymphatic plexus with overlying oedema ("peau d'orange"), which both carry a bad prognosis, whereas that of Paget's disease is good.

The histological varieties of carcinoma of the breast do not unfortunately indicate with any accuracy either the prognosis or the degree of hormonal dependence which is present. The natural speed of development of the growth is often shown better by the clinical story than by the degree of anaplasia or mitoses in the growth, though some guide is given by the amount of fibrosis around the growth, dividing the common scirrhous growth from the more dangerous cellular growths. This point of the importance of the natural history is underlined by the apparent paradox that very early treatment of a growth, though always desirable, is not always dramatically successful when compared with other growths; one rapidly growing, draws attention to itself quickly, is treated quickly, and yet re-appears in metastases; another slowly growing, is ignored for a time, treated late, possibly after metastases have occurred, and never re-appears. This difficulty is unavoidable, since one can

never compare the results of treatment of the same growth in two ways; human beings and their growths vary so much that it is not the same thing to compare two growths, however similar they are in their histology.

Two further points of interest, not peculiar to mammary growths, but well illustrated in them, are first the problem of delayed metastasis and secondly the importance of fibrous tissue reaction.

DELAYED METASTASIS. The traditional five-year interval after which a cancer is presumed "cured" is adequate to exclude the great majority of recurrences after surgical operation; but in a number of breast cancers secondary nodules may appear in the scar and elsewhere as much as twenty years later. Equally unsolved are the problems of where the cancer cells have been in the interval (i.e. did dissemination occur from the tumour and then lie latent, or has a small latent focus now disseminated), why the growth should have lost its vigour during the interval, and why it has regained it in the final flare-up of the growth; relation to hormonal changes in the patient are likely, but no evidence is available at all.

Equally surprising is the regrettable lack of study of the stroma of malignant growths, in particular the *fibrous reaction* and the presence of inflammatory cells in situations such as the breast where they are not likely to be related to surface ulceration and infection. If sections of breast cancers are examined it will be seen that in the centre there may be dense fibrous tissue with no cancer cells, while on the periphery the cancer cells are invading the fat without fibrous tissue; in the intervening zone the fibrosis is beginning. This fibrous tissue is not natural to the part; it is seen also around secondary deposits in the axillary fat and lymph glands, and it certainly abolishes the cancer cells in the centre of the fibrous mass; some of them look as if they were killed, but they are motile and it is not impossible that they have just moved out towards the periphery. But it would appear that this is in fact an inflammatory reaction to the presence of the tumour; comparison of large numbers of cases shows that the presence of this excess fibrous tissue makes a very large difference to the fate of the patient, though of course it must be conceded that the tumours with most fibrosis may be those with the slowest natural growth and therefore the most benign anyway. But the value of the fibrosis is not altered by this; and, moreover, it is the only apparent effective response. The lymphocytes and other attendant cells seen from time to time are not likely to carry "anti-cancer" substances; there is no positive evidence that they do, and cancer grows very easily in lymph-nodes in direct contact with lymphocytes. The histological picture suggests that

the cancer cell does not have an uninterrupted course, but is always just that little ahead of the slow fibrous response, and so keeps a winning lead.

CARCINOMA OF THE PROSTATE has several points of interest. First, the process is histologically extraordinarily common. Routine examination of prostates from elderly men in many countries have shown an unsuspected incidence of latent carcinoma from 33 per cent in the sixties to 75 per cent in the eighties. There are two main reasons why this has not been clinically appreciated long ago—one, that the growth is an extremely slow one, and slower still in extreme age; the other, that it occurs at the back of the gland, where it interferes least with the urinary bladder, and so is symptomless. This discovery arouses interest in what would be found in the way of latent cancer if exhaustive histological studies were made in other organs in the aged. Post-mortem examinations show a surprising amount of latent cancer.

The second point of interest is that like that in the breast this is a hormone-sensitive cancer, and even more strikingly so. Stilboestrol will keep the growth in hand for many years even after metastasis, and the proportion of hormone-dependent growths to the others is high.

The cancer cells are normally histologically well differentiated, and physiologically demonstrate this by secreting an acid phosphatase in quantity sufficient to estimate chemically in the serum when metastases have occurred. These metastases occur in two patterns—an extensive lymphatic spread, and a spread by the pelvic and lumbar venous plexuses to the adjacent bones, in which the deposits are unusual in that they excite extra bone formation; this interferes with the marrow and may lead to anaemia (p. 175); bone pain is common, but fracture unusual.

Special features of *carcinoma of the thyroid* are that it may occur in youth and childhood, especially after irradiation of the neck and chest; that the growths are often so well differentiated that they are hard to distinguish from the adenoma, but are usually papillary; that this good differentiation is so efficient that thyroglobulin is commonly formed; at least once secretion of thyroxin by secondaries has saved from myxoedema a patient who had had her whole thyroid removed for the primary.

Malignant Tumours of Glandular Surfaces

Carcinoma of the stomach lies a good second in frequency in men to carcinoma of the lung, and in women an even closer second to mammary carcinoma, a numerical importance that is increased by

PLATE 13. HYPERPLASIA AND NEOPLASIA

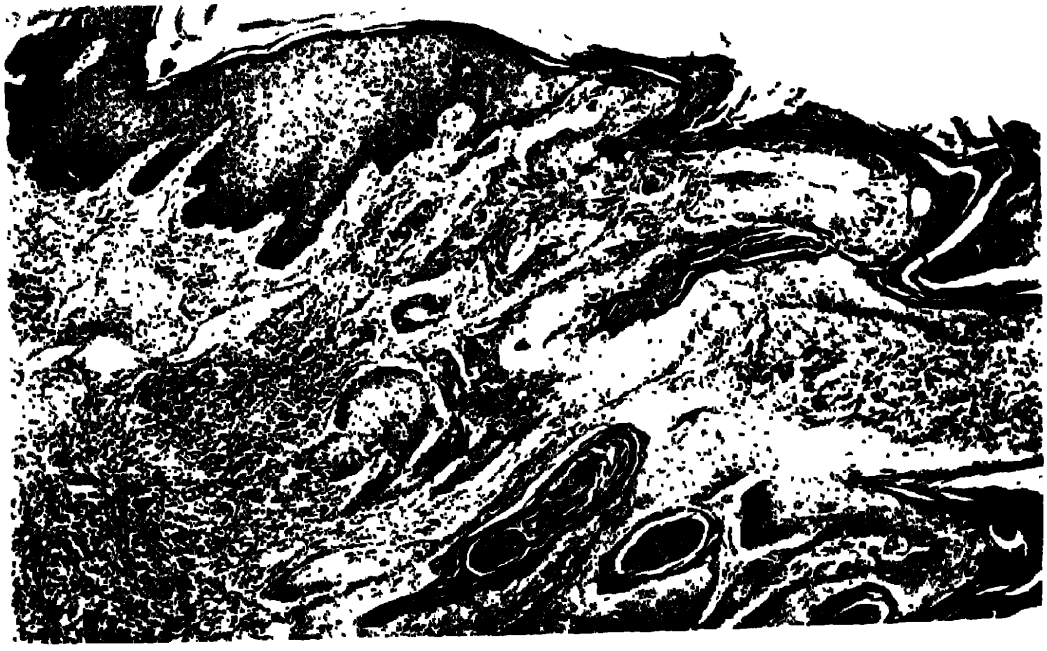
(*a*) Hyperplasia of skin (" corn "). The whole area shows great overgrowth of the cellular layers and thickening of the keratin; but in detail the differentiation of the cells is orderly, the keratin properly formed, with normal stratum granulosum, and the junction between epithelium and dermis is regular. This amounts virtually to the provision of an extra thickness of skin to deal with abnormal friction and pressure, and will disappear when not needed. × 30.

(*b*) Benign neoplasia (papilloma of skin; wart). A sharply localized area of skin has undertaken an apparently pointless overgrowth and is thrown up into papillae of keratin. This keratin is less well made, and so is breaking up, and locally there are persistent nuclei (parakeratosis) and other slight histological abnormalities. But though the epithelium is much thickened, the basement line is intact and sharp; it has been displaced into the dermis but there is no invasion.

(*c*) Malignant neoplasia (squamous-cell carcinoma of the skin). Again a local area of papillary proliferation of the epidermis but this time part of the growth is directed into the dermis and there is no sharp limit between the growing cells and the underlying tissue (invasion). The abnormal large nuclei of many malignant cells may be seen even at this low power (upper right). Clumps of invading epidermal cells grow and form their keratin in concentric laminated masses (" cell-nests " or " horny pearls ") (lower middle) there being no surface for desquamation. Keratin formation is imperfect with persistent nuclei and splitting of the horny layers; hence secondary infection, and the many small dark nuclei of inflammatory cells may relate to this rather than to the abnormal and often degenerate cells of the growth. × 40.

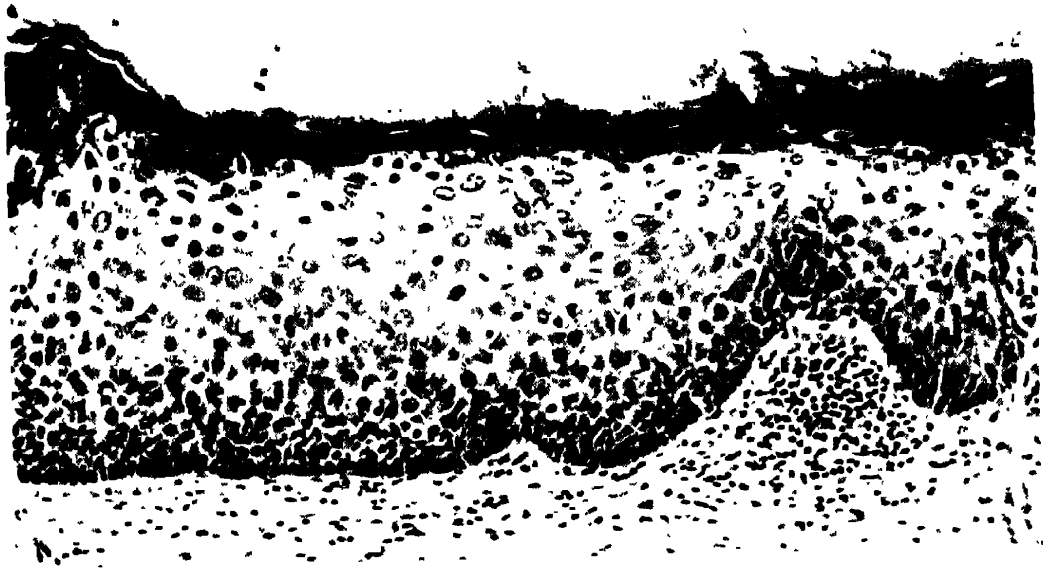
(*a*)

(*b*)



(*c*)

(*a*)



(*b*)

(*c*)

Plate 14. The Origin of Carcinoma

(*a*) Multifocal origin of basal-cell carcinoma of the skin. Three foci, separated by normal epithelium, can be seen where downgrowth of the basal cells has occurred; in the right-hand focus, the origin involves a hair follicle, in that on the left the characteristic histological feature of this kind of invasive carcinoma can just be made out—a " palisade " of basal cells. By the time the tumour is clinically treated, these are commonly confluent (the black at the bottom is haemorrhage from the surgical excision). × 20.

(*b*) Atypical " pre-invasive carcinomatous change " in biopsy from vulva. The basement line is sharp and this cannot be called malignant invasion. But the nuclear characters of the middle prickle layer are so unlike those found normally, include hyperchromatic and giant nuclear forms, and the differentiation to normal surface cells is so imperfect that this epithelium is classed as " atypical."

The terms " precarcinoma " or " pre-invasive carcinoma " are used in accordance with the site under examination, the experience of the observer, and all that is clinically known about the outcome of this kind of growing epithelium. In the vulva, this is a notoriously dangerous change, and the subsequent development of invasive carcinoma was thought probable. × 200.

(*c*) Invasive carcinoma. Excision was carried out a few weeks later, and about an inch away from the preceding section invasion can now be seen; there are clumps of cells in the subcutis, and two bulges in the basement line of the epithelium suggest that further break-through is likely. × 200.

The changes seen in these sections all suggest that the carcinomatous process involves a considerable area of tissue in its earliest stages.

the poor results of treatment. Causing symptoms by impairment of gastric secretion and motility, which lead to loss of appetite, and by pyloric obstruction, it is often found to have spread to glands or to peritoneum by the time surgical exploration is undertaken.

Search for the cause in humans of a common growth like this is started by an investigation into the distribution in different classes of people. The geographical incidence is not uniform; Holland, Japan and Czechoslovakia have a higher rate than the rest of the world, where figures are available. In Britain, there is an unexplained association with North Wales, and another with blood group A. There is a distinct social grading, the lower income groups being more affected than the upper, and the wives as well as the husbands show this, so it is not likely to be associated with industrial hazards. These points suggest a dietary origin, and a possible association with overcooked fatty food; this point was investigated by Kennaway, who had been a pioneer in the chemical analysis of carcinogenic tars (p. 248), and he has extracted carcinogens from a number of "overcooked" substances, but animal experiment has been unsuccessful in proving this origin. It is a very uncommon tumour in animals, even allowing for the limited age that most animals attain either in wild life or in farms; and it also appears uncommon in uncivilized peoples, where again the same points of age distribution and inadequate death statistics arise.

The slightly less common carcinomas of the large bowel are not at present assignable to any cause, except the few in which a genetic defect, the formation of polypoid mucous membrane, is known, or those which follow ulcerative colitis.

One exception to the generalization that function and low malignancy go together in carcinoma is found in both gastric and colonic mucus-secreting growths—so-called mucoid or colloid cancers. Although mucus secretion may be so intense that many tumour cells drown themselves in the middle of it, the growths as a whole are of considerable malignancy.

CARCINOMA OF THE LUNG. Thirty years ago the observers who drew attention to the increase in frequency of this growth were told they were imagining things and that the increase was due to better diagnosis or improved histological classification. Although in the past this growth was often buried in the group of "sarcoma of the mediastinum," there is no doubt now that it was a rare growth up to about 1930 and since then has reached the head of the list in male cancer and is still increasing; it is now a medical problem of the first magnitude. Kreyberg in Norway has shown that the label "carcinoma of the lung" covers two diseases, histologically and

otherwise separable into *adenocarcinoma* with an equal sex incidence, and not increasing very much, and *squamous-celled* (including the undifferentiated varieties spheroidal- and oat-celled) with an overwhelming male sex incidence. This is the new disease that is responsible for the increase.

Strong statistical evidence associating this with the habit of smoking cigarettes (rare till the 1914–18 war, and a predominantly male habit till about 1930; the lapse of time representing the possible incubation period of a carcinogen (p. 248)) is equally strongly rebutted by those with personal or financial interests in tobacco; the truth is hard to assess, and may depend on such apparently minor points as the length of the butt or the use of filters or holders which lower the temperature of the smoke and condense carcinogenic tars in it. Other inhaled carcinogens in town air, derived from smoke, road tar, petrol fumes, have been incriminated; haematite dust, asbestos and the radioactive air in mines in Bavaria are known causes.

The pattern of metastasis is unusual. Although it includes the standard lymphatic and pleural routes, blood-stream spread is early and may be in advance of any local effects. This is particularly important since the brain is a favoured site of such secondaries; the adrenal is also favoured, but this is only of pathological interest and not of clinical importance.

As well as secondary deposits, the nervous system may be affected by obscure changes which at present can only be vaguely described as toxic " carcinomatous neuropathy " including symptoms suggesting polyneuritis or myopathy.

CARCINOMA OF THE KIDNEY is of interest for two particular points. The route of metastasis is almost entirely the blood-stream; the growth pushes into the renal vein and so to the lungs and the general circulation, favouring the bones. The appearance of these growths is striking, with much lipoid, and areas of necrosis (venous infarction) and haemorrhage, and histologically with tubules of clear cells recalling adrenal cortex. For a long time they were thought to originate in ectopic fragments of that tissue (whence their alternative name *hypernephroma*); they are sometimes called Grawitz' tumours, after the originator of this theory; but they never show endocrine effects and can be shown to arise from the renal tubules. Carcinoma arising in the renal pelvis, like that arising in the bladder, is a transitional- or squamous-celled epithelial carcinoma that is orthodox in appearance and behaviour; though multiple foci in these epithelia are very common, it is not yet certain whether this is implantation of

metastases, spread of a carcinogenic material in the urine, or primary multifocal origin.

CARCINOMA OF THE LIVER, which like that of the kidney metastasizes preferentially by the blood-stream, may be derived from the intra-hepatic bile-ducts, but the more interesting and commoner variety is that in which the regeneration nodules of a cirrhotic liver change to a neoplastic pattern of growth; the neoplastic cells retain enough of their normal physiological function to secrete bile, even in secondary deposits (Plate 15).

Tumours of Supporting Tissues

BENIGN TUMOURS. These are found in most of the connective tissues of the body. In the blood-vessels, the growths are more malformations than true neoplasms, growing proportionately with the growth of the patient; the complex development of blood-vessels, which makes arterial anomalies so common, produces "hamartomas" (a tumour arising through developmental error is known as hamartoma) which are disfiguring on the surface and provide an inadequate supply of blood to the part they serve; surgical treatment may remove the disfigurement but will usually not improve the blood supply. The tumours are known as *angiomas*, with the prefix haem- or lymph-, and adjectives describing the size of the abnormal channels capillary, venous, or commonly cavernous, where they are made up of spaces with fibrous walls.

More definite tumours are the *fibromas*—encapsulated masses of fibrous tissue found most commonly in the skin, ovary, bone, and under the buccal mucosa. *Lipomas* may occur in adipose tissue anywhere, usually in the subcutis or intermuscular septa. Both these form encapsulated lumps, histologically and to the naked-eye exactly like their parent tissue, and cause trouble either because they are unsightly or because they press on important structures. The *keloid* is not a true tumour, but an excessive hyperplasia of fibrous tissue in a scar.

The *neurofibroma* is another common example of the group; it is usually a misnomer, arising from the sheath of Schwann and not from the fibrous tissue of the nerve. The neurilemma cells are concerned in myelin formation, and these neurofibromas hold a considerable quantity of fat and may become cystic. They may be found attached to any nerve, often intercostal, but the most important members of the group are those found on the posterior roots of the spinal nerves, and on the cranial nerve VIII and more rarely on V and IX. Their situation here leads to pressure effects of great importance.

Another exceedingly important and common tumour is not quite satisfactorily described by its common title " fibroid " of the uterus. Its full name, *fibromyoma*, is better but it is essentially a smooth muscle tumour or *leiomyoma* with fibrous tissue incorporated in it, and becoming the more important component as the muscle undergoes atrophy later. These are often massive tumours, often multiple, found mainly in the uterus, but sometimes elsewhere in the female genital tract. Apart from size and pressure effects, the fibroid enlarges the surface of the endometrium and increases the loss at the menstrual period; if it is in the cervix it may interfere with the urethra or with parturition.

In spite of the frequency with which this tumour occurs, little is known of its causation. It is hormone-dependent, undergoing atrophy at the menopause, and has been induced in animals by oestrin administration.

Leiomyomas arise also from the alimentary tract, and usually remain typical benign tumours. They have a tendency to undergo cystic changes and cavities in them may come to communicate with the lumen of the gut.

Voluntary muscle, unlike smooth muscle, is the rarest possible site for tumours of any kind; the intermuscular septa rather more often give fibromas and fibrosarcomas; in spite of the large mass provided for the reception of blood-borne secondary growths of all sorts, they are again exceptional (even allowing for the limited amount of muscle that is surveyed at the usual autopsy). This is the more surprising because growths spreading directly into muscle grow readily.

Bone again rather rarely produces true benign tumours growing from the mature tissue. A dense *ivory osteoma* from the skull is the least rare. Cartilaginous tumours are not so rare; the *ecchondroma* projects to the exterior of the bone, and is often multiple around joints as a curious mainly sex-linked male abnormality of growth; these ossify in adolescence just as other epiphysial cartilage does and then cease to grow as a rule, though the bony mass (exostosis) may interfere with joint movement. *Enchondromas* are situated inside the bone; they ossify much less obviously. The fingers and pelvis are favoured sites. A considerable number of varieties of benign tumours in which bone, fibrous tissue and cartilage are mixed have been described; reference must be made to special texts for all except that known as *osteoclastoma* or giant-cell tumour. This is found in the young adult epiphysis, forming a rounded mass with a thin shell of bone outside it, which is laid down by the periosteum as fast as it is eroded by the tumour within. The centre is soft, maroon from

haemorrhage, and histologically is identifiable by a combination of spindle cells with multinucleate giant-cells compared to osteoclasts but much larger. A special very benign example is found in the gum (" myeloid epulis ") in association with destruction of the roots of deciduous or permanent teeth or in relation to the demand for calcium in pregnant women.

MALIGNANT TUMOURS. As a whole, this group of *sarcomas* is very much rarer than the group of carcinomas—about 1:100. They have in common a soft cellular texture, creamy white except where necrosis or haemorrhage have occurred, without the granularity of carcinoma; they are traversed by numerous ill-formed blood-vessels, by which they tend to metastasize to the lungs rather than to the local lymph nodes. The degree of malignancy varies; in general they tend to be very malignant, but in the fibro-sarcomas some will recur and invade locally for a long time before metastasizing. Their origin in connective tissue often with ill-defined landmarks may make invasion hard to determine, and pronouncements on their malignancy may have to be based on atypical cells, which are usually fairly easily compared with the tissue normal for the part.

Some benign groups are so rarely represented by malignant tumours that they may be dismissed at once. Liposarcoma, angio-sarcoma, rhabdomyosarcoma are infinitely rare. *Leiomyosarcoma* and *neurofibrosarcoma* are both known as developments from the sites where the benign tumours are common. Two forms of sarcoma alone are sufficiently likely to be seen to merit description.

(*a*) Fibrosarcoma may develop from fibrous tissue anywhere, least rarely from intermuscular septa and the foot. The masses at first may suggest pure fibroma, but any tendency to softness, cellularity, or mucoid change (so-called myxoma or myxosarcoma) should arouse suspicion.

(*b*) Osteosarcoma turns up at two main times of life—from 5 to 25, when the epiphyseal regions at the knee and elsewhere are affected; the tumour is a painful, rapidly growing mass which both forms bony spicules in its substance and destroys the original bone; a little periosteal reactive bone is usually added but the defensive mechanism is very poor. Then later in life in the 35 to 55 age group massive slowly developing *chondrosarcoma* is known, sometimes arising from the benign chondromas of the pelvis and femur. The frequency with which sufferers from extensive Paget's osteitis deformans develop bone sarcoma has been commented on.

Secondary tumours in bone from carcinoma are, however, commoner than all these put together. They may come from prostatic primaries, in which case, as in a small proportion of

mammary growths, they form bone (osteosclerotic); the majority of mammary growths, and those from other sites (lung, kidney, thyroid, commonest) are all osteolytic. The spontaneous fractures resulting may heal; those from primary tumours do not.

Glioma

The majority of primary nerve-tissue tumours fall into the group of benign and malignant gliomas. Much specialist labour has been put into the histological description of these tumours, but here we must confine ourselves to the commoner groups, the benign glioma usually derived from astrocytes and called *astrocytoma* and the undifferentiated growth for which the old name gliosarcoma has been replaced by *glioblastoma multiforme.* The astrocytoma occurs in two favoured sites, the lateral lobes of the cerebellum in children, and the cerebral hemispheres in adults; in the first it is more likely to be cystic and well-defined, in the second it tends to ill-defined growth and shades into the malignant tumour.

Glioblastoma multiforme is a soft ill-defined haemorrhagic and necrotic mass found in the cerebral hemispheres of adults most frequently, where its rapid growth, tendency to haemorrhage and oedema around it, and its position give it a clinical picture that suits its name " multiforme " as much as its naked-eye and histological picture do. Its rapid growth and vascularity are points of resemblance with sarcoma, from which its main difference is the fact that its metastases are confined to spread through the cerebrospinal spaces, which sometimes occurs; spread outside the C.N.S. is unknown, in spite of its vascularity and malignancy. We know nothing about the causes of these growths.

It is convenient to complete the survey of neural tumours here. The fully mature nerve cell does not multiply and so is not involved in tumour formation; the primitive neuroblast does, however, give rise to three malignant growths: that in the retina (known also as glioma and neuro-epithelioma), which is one of the best examples of a growth determined by the chromosomes of the sufferer; that in the cerebellum, known as the medulloblastoma, which is the least uncommon of them and which demonstrates spread by the cerebrospinal fluid better than any other tumour; and neuroblastoma of the adrenal medulla (sympathicoblastoma; better differentiated varieties, ganglioneuroma). All are tumours of children and young adults; all form white soft cellular masses with the cells sometimes arranged in rings (rosettes); all are malignant and rapidly growing, usually partly radiosensitive growths. The widespread secondaries of the adrenal tumour, disseminating to bones, glands, liver and

elsewhere, may provide a puzzling clinical problem with a difficult primary to locate.

The important *neurofibroma* (p. 234) which may be found inside the skull and spinal canal, and the *meningioma*, a benign tumour from the arachnoid granulations, complete the list of common primary tumours affecting the central nervous system.

But as in bone, secondary deposits from carcinoma, notably pulmonary carcinoma, are a very important section of intra-cranial neoplasms.

Melanoma

Melanin-forming cells are found in two important situations in the body, namely the skin and the choroid of the eye, and other less important sites are the meninges and the buccal mucosa. Their protective function in the defence against radiation in the skin has been alluded to (p. 116) as has the general question of pigmentation by melanin (p. 209).

The embryological derivation of these cells appears to be from the neural crest of the early embryo, from which they migrate to their definitive positions. Those in the skin take up their position on the outer surface of the basal layer of cells, over many of which they spread and make contacts and so transfer the melanin to the basal cell. These *melanoblasts* frequently either migrate back into the dermis or fail to complete their migration out of the dermis, and then form pigmented plaques or masses (with or without smooth muscle and hair and neurofibromatous accompaniments) which are described as *melanomas* (one form of birthmark or *naevus*; these two terms are also used to include angiomatous malformations). By far the greatest majority of these melanomas are benign; they may be cosmetically undesirable, for like many malformations they grow with the patient, and can be regarded as benign tumours; they are so common that few people are without one or two.

MALIGNANT MELANOMAS OF THE SKIN arise rarely, but they are serious. Preceding benign tumours are often present; the change is indicated by growth of the mole after adult life, ulceration, an injected rim round the tumour; these frequently injured are more likely to change, and those on the hands and feet are often malignant from the start. The change to malignancy is quite exceptional before puberty. Histologically, the presence of melanoma cells on the border between epidermis and dermis (junctional melanoma) is an indication of possible malignancy, those entirely dermal rarely changing. Metastasis by the lymphatics occurs early, and subsequently wide dissemination with many small tumours in many

sites, including skin and mucosal surfaces. This tumour is almost unique in crossing the placenta to the foetus; its growth is much accelerated in pregnancy.

MALIGNANT MELANOMA OF THE EYE (sometimes separated as melanotic sarcoma) is a tumour of adult life. It differs from the skin variety in not having any benign counterpart; in having a more spindle-cell structure; in metastasis being more likely to produce large hepatic secondaries, and often after a notable lapse of time since the removal of the primary—a thirty-two-year gap has been recorded.

The degree of pigmentation may vary greatly even in one growth and its secondaries; the unpigmented members are difficult to recognize, and should be considered in the diagnosis of unusual skin masses.

Neoplasia and Hyperplasia in Reticulo-endothelial Tissues

The primitive reticulum cells of the marrow, spleen, lymph-glands, Kuppfer cells of the liver, are the parent cells of three groups of functional mature cells—

1. The *phagocytic mononuclear* cells, resting and active.
2. The *haemocytoblasts* (precursors of the blood cells); *plasma cells* (forming antibodies); *lymphocyte* (function unknown). This group can be bracketed as haemopoietic.
3. The fibrous tissue cells.

There is still argument about how far these cells, once having become determined for one function, can switch to another; both in health and disease the whole system shows unexpected linkages which suggest that although every cell cannot change into each of the other types, the more primitive cells have their paths of differentiation left open to them, and some more mature cells at least may take up other functions than that for which they appear to be histologically equipped.

It will be noticed that these are the cells which are mainly concerned in the formation of an inflammatory response, and the proliferation that occurs in inflammation is characteristic of that kind of growth referred to as hyperplasia. It affects a functional part of the system, that draining the infected focus; it is physiological in that the cells keep their appearance and their reactions; it has an obvious purpose in the life of the organism; and it ceases when the stimulus is disposed of. But even in a hyperplastic response, in this system the overgrowth is less localized; the whole of the bone marrow takes part in the maintenance of a leucocytosis, and the phagocytes of both spleen and liver may be mobilized in a general

infection. This tendency to generalize is seen in the neoplasms affecting these tissues as well as in their hyperplasias.

Benign tumours are known, though not common or important; local nodules of lymphoid tissue, like small lymph-glands in appearance, are found in the mucosa of pharynx and rectum and are called *lymphomas*.

An intermediate form about which there is argument is conveniently called *Hodgkin's disease*, commemorating the first observer of this group of diseases and prejudging nothing about the cause or relations of the process. The primary focus is usually in a lymphatic gland, which becomes painlessly enlarged without any obvious exciting focus in the draining area or any change in its neighbours. Adjacent glands are soon involved, by a process of spread which leaves the outlines and capsule of the glands intact, so that they remain clinically discrete. Because of this absence of invasion, some authorities class this as a benign process, but the further clinical course of the disease is far from benign, and the dissemination that takes place next is like metastasis, unusual only in that the sites chosen are mostly, though not exclusively, organs of the reticulo-endothelial system. Deposits (or possibly fresh independent foci) of neoplastic cells appear in the spleen, bone marrow, lymph-glands, lung and elsewhere, alike in their histology to the lymph-gland first involved. This spread makes the common name " lymphadenoma " unsuitable.

In all cases and all situations the important growing cells are atypical reticulum cells, varying a good deal in their morphology but characterized by tumour giant-cells of an easily recognized type, first described by Greenfield in 1872 but now usually known as Dorothy Reed giant-cells (Plate 16). In addition to them, many other cells are habitually present, some derived from the normal cells of the gland, others immigrant and some possibly derived from differentiating reticulum cells. The most characteristic and almost diagnostic invaders are eosinophil leucocytes which may be present in numbers. With all this proliferation the normal structure of the gland is first distorted so that the germinal follicles are displaced and then obliterated, this being accompanied by a great deal of fibrosis.

Pressure from glandular masses in the abdomen and mediastinum leads to death, assisted by symptoms which at present can only be labelled toxic: pyrexia, asthenia, anaemia.

The aetiology of this disease is not known. No organism has been demonstrated in sections or by culture which satisfies any of Koch's postulates; there is no clinical evidence of contagiousness; no

animal vectors are known. The disease is so uncommon (though it is the commonest individual in the group) that it would be difficult to trace a living agent from case-to-case. Some clinical features, such as the pyrexia, and the fact that the cells involved are those concerned with inflammations, have led people to look for an infective origin, and it has been called lymphogranuloma for that reason. But it has the characters of a neoplasia and not a hyperplasia; there is no reason why the cells concerned with active growth in one function should not show active growth in another way, and most present authorities regard the disease as a neoplasm of the reticulum cells of the glands, though they explain the other cells found in the glands in various ways. Even if the masses are non-invasive, they have the other two features of malignancy, atypical growth and metastasis.

A number of rarer conditions are described under the general term reticulosis, affecting the lymph-nodes and the blood-formation and destruction; references are given to sources where they can be studied, as they are too rare for inclusion here.

The frankly malignant growths are classified as *lymphosarcoma*. These invade as well as metastasize, and their malignancy is undoubted. As a disease, the process is more acute than Hodgkin's disease, the glands are softer and they have outlines blurred by the invasion through their capsules. They arise as often in the lymphoid tissue of the alimentary tract as in the glands; Hodgkin's disease is very rare in the alimentary tract. The small-celled group is very prone towards the end to spill over into the blood-stream, and conversely many lymphoid leukaemias, beginning in the blood, form sarcomatous masses; there is convergence here between the two processes.

Reticulosis is a term used at the present day with an extremely wide connotation, some authors using it to cover inflammations (which are undoubtedly processes in which the reticulo-endothelial system is involved) and leukaemias. Used as widely as this the term loses its value, but a case can be made out for including the storage-reticuloses, where various lipoids are concentrated in cells some, though not all, of which are reticulo-endothelial.

Leukaemias

Fully deserving a heading of their own in spite of their close relations to the preceding conditions, these abnormal proliferations of the marrow are important fatal diseases, becoming increasingly common at present. In all kinds of the leukaemias, abnormal cellular proliferation in the marrow is invariable, and the diseases

are system diseases in that the whole of the haemopoietic marrow is usually involved before the end, though in one of the group, myelomatosis, clinical evidence of a primary site is not unusual. As well as abnormal proliferation in the marrow, abnormal cells may occur in the circulating blood, very rarely in myelomatosis, nearly always in the others, but absent in the " aleukaemic leukaemias." Although the most obvious changes are in the white blood-cells, which have given the disease its name, the erythropoetic marrow is depressed and platelets are affected, features responsible for much of the fatality. In spite of the name, these must be considered diseases of the blood as a whole. Four headings will be used here for simplicity—

1. Acute leukaemia: primitive cells usual in the blood.
2. Chronic myeloid leukaemia: polymorphs and their precursors in excess in the blood.
3. Chronic lymphatic leukaemia: lymphocytes in excess in the blood.
4. Myelomatosis: plasma cells very occasionally in the blood, globulins derived from them are usual.

1. THE ACUTE OR STEM-CELL LEUKAEMIAS. In these the predominant abnormal cell in the peripheral blood may be so primitive that its matching out of the series of normal white cell precursors is difficult; on small cytological differences they may sometimes be grouped as myeloblasts or lymphoblasts, or occasional more mature cells may be recognizable; this distinction makes a little difference in that the lymphocytic variety responds to cortisone, but even experts often compromise by the use of the term " blast-cell " or stem cell.

The untreated diseases have a fatal course of a few weeks to months. Presenting symptoms derive from the effects of the process on all marrow elements; the red cell damage leads to a severe and rapidly progressive anaemia; reduction in the platelets produces purpuric haemorrhages, often following dental extraction and commonly the terminal event; the abnormal white cells bring about deficient inflammatory responses, so that ulceration of the gums is common, and infiltrate widely in many tissues. The symptoms are insidious and often misleading.

2. CHRONIC MYELOID LEUKAEMIA, the commonest member of the leukaemias, begins equally insidiously; the earliest cases picked up are found to have an unexplained polymorphonuclear leucocytosis when blood-counts are done either from a complaint of *malaise* or sometimes in other routine examinations. The symptoms may, however, be so tolerated that the patient comes up with an abdominal

lump, which is a painless but often considerably enlarged spleen. The progress of the disease is that of a moderate anaemia, with steadily increasing number of white cells in the blood; at first these are fairly mature, with only a few myeloblasts, but gradually the primitive cells outnumber the more mature, and the disease may end in an acute termination about five years from its apparent onset. The size of the numerous white cells, of which there may be 250,000-400,000/mm^3, and the increase in the platelets that is often found brings about an increased viscosity of the blood and a tendency to thrombotic incidents.

3. CHRONIC LYMPHATIC LEUKAEMIA is associated with lymphocytic excess in the blood, bone marrow and spleen, which is enlarged, as are the lymph-glands. Anaemia is less, but the platelets may drop; infection is poorly resisted, and the disease is fatal in a few years.

There is evidence associating all forms of leukaemia with excessive exposure to radiations—atomic warfare, medical and industrial radiology—and to other marrow poisons.

4. MYELOMATOSIS. Foci arise in the haemopoietic marrow, rarely single, and often nearly confluent throughout at the end of the disease, of plasma cells or undifferentiated plasma cell precursors; the alternative name plasmacytoma is often used. Bone pain and multiple fractures result; excess globulin is present in the blood, and often excess calcium; the kidney shows tubular lesions, and the patients die from the effects of the fractures—paraplegia, becoming confined to bed, bronchopneumonia, or from uraemia. Abnormal proteoses (Bence-Jones) are often present in the urine.

Much research is still required on the cause of all this group of diseases.

Complex Tumours

Included in this group are tumours arising from cells that are capable of giving rise to more than one type of tissue in the course of their differentiation. They are only a more extreme example of the variation in differentiation that can be found in different parts of the same tumour, more particularly the malignant tumours, where for example a bone tumour can give rise to fibrous tissue, osseous tissue of various kinds and cartilage; but the present tumours can give rise to tissues less closely related, and often derived embryologically from more than one germ layer in normal development. The general term *teratoma* (" tumour arising in a monster ") is applied to these tumours in which more than two germ layer tissues are present; the term *teratoblastoma* is sometimes used

for the small group with two layers only. These tumours may develop from—

1. Embryonic cells whose maturation is postponed and which develop when free from embryonic controls into malignant tumours, e.g. the Wilms' tumour of the kidney or nephroblastoma; this apparently represents two germ layers (epithelial and muscle tissue present) but is derived from the metanephros, which can itself develop into renal tubules and glomeruli and the peripelvic and ureteric muscle.
2. Embryonic tissues displaced in development, maturing in their misplaced position into jumbles of tissues which grow in size, but are not necessarily malignant in growth pattern, e.g. the teratomas of the thorax or sacral regions.
3. Tumours derived from the germ cells of the testis.
4. Tumours derived from the germ cells and germinal epithelium of the ovary.

The reason for the development of these cells into tumours, often of a high degree of malignancy, is unknown. In the first two groups, differentiation and malignancy are related inversely; the most benign are the conjoined foetal masses found now and then attached to otherwise normal foetuses, and reaching their extreme form in "Siamese twins." The better formed the tissues, the older the patient, the more benign the behaviour and the more likely the tumour to be represented by a cyst lined with skin (dermoid cyst). The sacral ones in infancy are apt to be undifferentiated and invasive (as is the *chordoma* derived from notochord remnants and found in the sacral and occipital region).

The teratoma of the testis is a tumour found in young adult life in which the spermatogonia have undergone spontaneous development to form a mass of poorly formed tissues in which cartilage and an aberrant type of respiratory epithelium with muscle round it are prominent, among very variable barely recognizable copies of the structure of other adult and embryonic tissues: the cysts of the epithelium give rise to the old name of fibro-cystic disease of the testis. In spite of the differentiation the behaviour is that of a very malignant tumour, metastasizing both by lymphatics and bloodstream. The differentiation may be sufficient to produce hormones with physiological effects on the patient and excretion of gonadotropic hormone in the urine (chorion-carcinoma of the testis). A less differentiated tumour of the spermatogonia also occurs, *seminoma or spheroidal-celled carcinoma* with much the same clinical course. Both are more frequent in the imperfectly descended organ.

Unlike those of the testis, the teratoma of the ovary is cystic and benign. Skin and its appendages are so largely represented that the name *dermoid cyst* is given; bone, teeth, nervous tissue and intestinal and respiratory epithelium are common and almost every tissue of the body has been recorded, sometimes one tissue (thyroid in the *struma ovarii*) to the exclusion of the rest; but it is characteristic that the histological structure is very good; no anatomical structures are found, however, and the masses have no symmetry or polarity.

In addition to the dermoid cyst, two other common cystic tumours of the ovary are found derived from the germinal epithelium. Slightly the commoner is the unilocular papilliferous serous cyst; the other, the multilocular pseudomucinous cyst, reaches a greater size through the accumulation of intra-cystic fluid like a mucin. The growth of both these tumours may follow a malignant pattern with metastases across the peritoneum and in the glands and elsewhere, the papilliferous one much the more commonly. For the interesting variety of solid tumours derived from the ovary reference must be made to the specialist books; the fibroma and the solid secondary carcinoma called after Krukenberg are the commonest; the tumour derived from the cells of the Graafian follicle, the granulosa-cell tumour, is notable for producing a significant quantity of oestrogenic hormone in both its benign and malignant type. The others are rare.

The Aetiology of Neoplasia

A very great deal of work and very large sums of money are at present being devoted, and have for many years been devoted, to the search for a cause for malignant growths. If successful, this would be likely to help greatly in preventing the disease, though it would not necessarily lead directly to a cure. The discovery of the tubercle bacillus—if it and not the patient can be for the moment taken as the cause of the tuberculosis—long antedated the discovery of a cure, but it did make the search for a cure possible, because it isolated a factor in the production of the disease which was amenable to experimental animal and bacteriological study. It is possible that such a factor will emerge from search for the cause of cancer; the search has already resulted in many causes of cancer being discovered, though no unique cause. But these experimental causes also can be used to produce standard animal growths in which attempts at chemotherapy and other investigations may be undertaken.

The difficulty in finding the cause of human cancer is illustrated by certain points arising from animal study.

PLATE 15. FORMS OF BENIGN AND MALIGNANT GROWTH

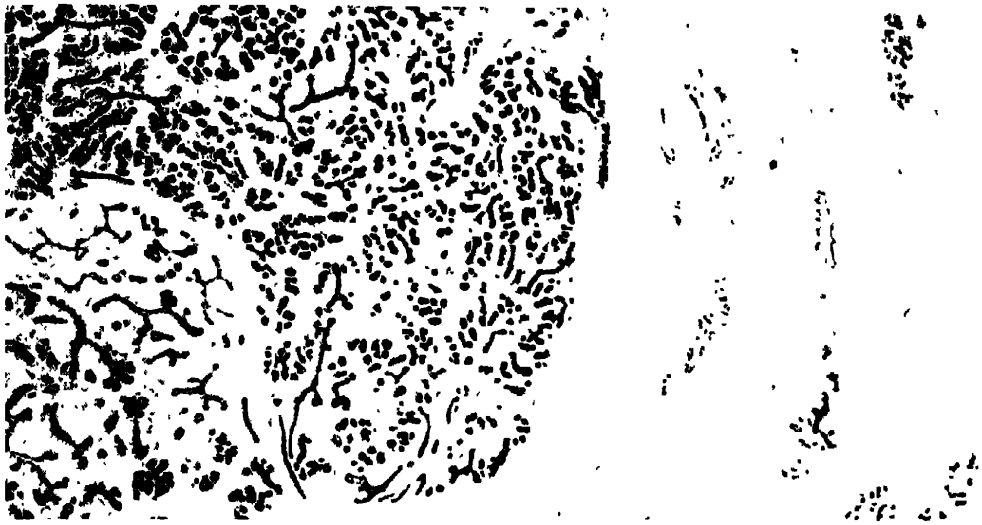
(*a*) (*b*) Low power (× 20) to compare the different outlines of benign and malignant tumours of the breast.

Normal mammary tissue to right. In (*a*) there is the edge of a smoothly rounded mass lying to the left, composed of orderly interlacing bundles of fibrous tissue and epithelial cells ("fibro-adenoma"). The demarcation between normal and abnormal is perfectly clear and sharp and the mass will shell out of the normal if the surgeon obtains the correct plane of cleavage.

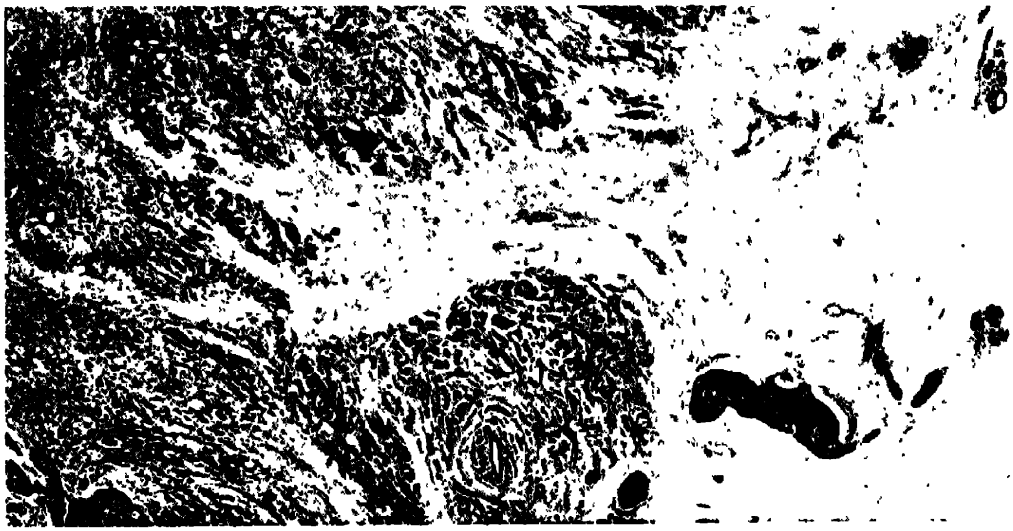
In (*b*), however, the proliferation is made up of a disorderly mass of epithelium and fibrous tissue with an irregular edge of invasive columns of cells, especially in the upper half. No plane of cleavage exists. There is a dilated lymphatic space containing a clump of tumour cells; this is a tumour embolus *en route* for the axillary glands. The tumour epithelium is not making any structures resembling mammary acini and can therefore be classed as poorly differentiated; there is little fibrosis in the tumour. This is the ordinary carcinoma of the breast sometimes called carcinoma simplex.

(*c*) Higher magnification (× 170). Rounded outlines do not necessarily indicate benign tumours. They will also be found when a rapidly growing malignant tumour develops in a soft tissue.

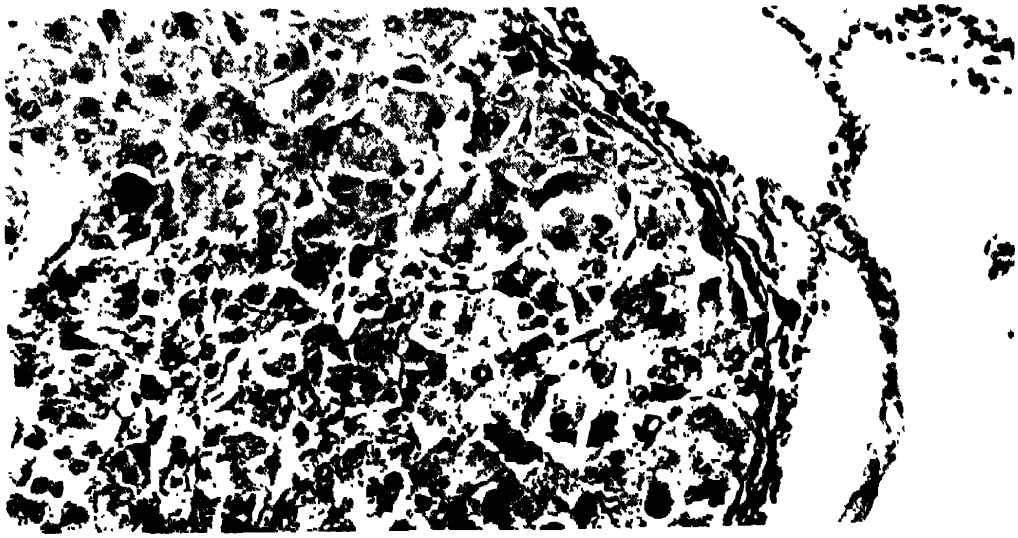
This is a lung secondary deposit (alveoli to the right), which commonly is of this form, growing by displacement rather than invasion ("cannon-ball secondaries"). This example is from a carcinoma of liver; the cells are recognizable as liver cells, and plugs of bile can be seen among them. Although therefore apparently benign in outline, and physiologically so well differentiated that it has one normal function at least, this is a metastasis, and, by definition, malignant.



(*a*)



(*b*)



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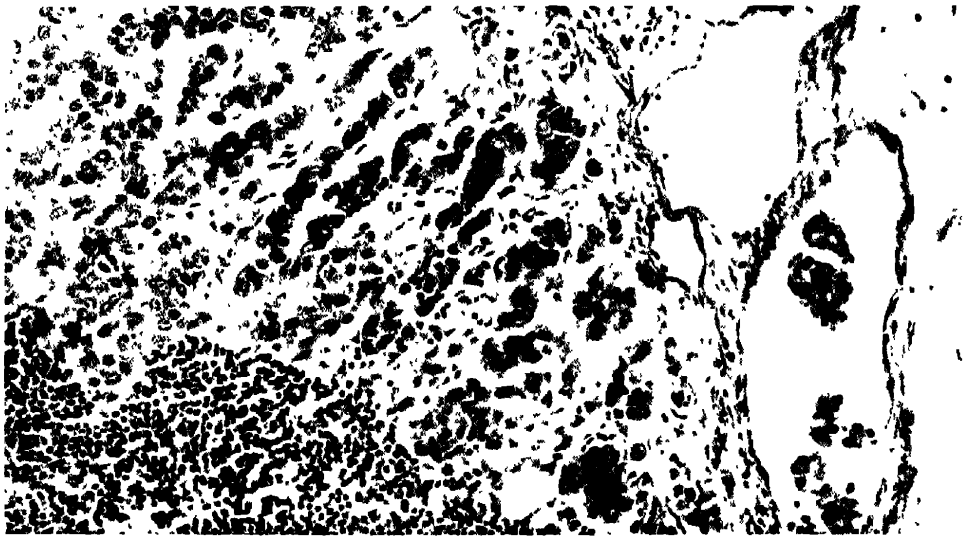

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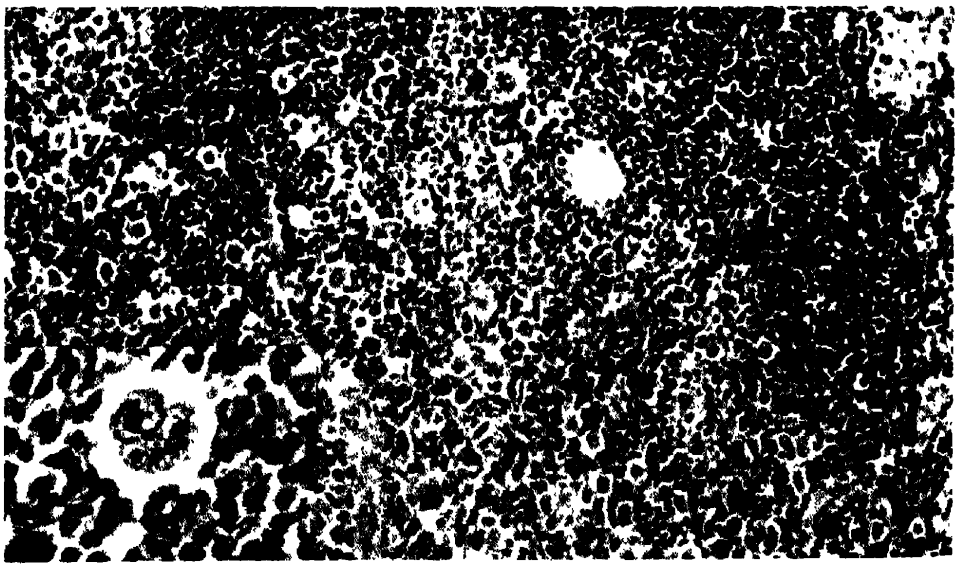

(*c*)

PLATE 16. LYMPH-NODE ENLARGEMENTS

(*a*) Inflammatory hyperplasia. Proliferation and accumulation of inflammatory cells in the sinuses results in separation of the lymph-follicles by widened sinuses (sometimes referred to as " sinus catarrh "). Though not present in this specimen, large germinal centres may be seen in these follicles. Higher magnification identifies the cells in the sinuses as macrophages (cf. Plate 4), lymphocytes and a few polymorphonuclear leucocytes. × 120.

(*b*) Secondary carcinoma (axillary lymph-node, primary carcinoma of the breast). The malignant cells arrive in the afferent vessel (seen leaving the breast in Plate 15) and colonize first the peripheral sinus, gradually spreading through the gland. The cells are immediately in contact with the lymphocytes and yet remain healthy, which does not suggest any hostility on the part of the lymphocytes. Fibrosis is already beginning between the columns of carcinoma cells. Note that they are very much larger than the other cells in the node, both lymphocytes and macrophages; this point helps in recognition of smaller or less differentiated foci of growth from macrophage hyperplasia. × 120.

(*c*) Hodgkin's disease. Proliferation of medullary reticulum cells of varied cellular appearance is displacing the follicles to the edge of the node and may obliterate them. Mitotic figures and large atypical macrophages can be made out at this magnification; higher magnification would show nuclear patterns of " Dorothy Reed " cells (inset), and eosinophil leucocytes are conspicuous in stained slides. × 140 (inset × 450).

1. Painting animals with tar produces cancer, and very exact chemical analysis of some cancer-producing substances (carcinogens) has been carried out so that some of quite simple chemical formula are known (methylcholanthrene, β-naphthylamine, β-propiolactone for example). Now substances of this kind may cause cancer after the application of minute amounts (0·5 μg of dibenzanthracene) and after the lapse of a time that corresponds to ten years in man. The cause and the effect are long separated and the cause is quantitatively trivial. Elucidation from a patient of a history of exposure to a gramme of a chemical substance ten years ago is not likely unless the exposure was very unusual. The link between X-rays and carcinoma was quickly recognized when X-rays were unusual; the possible link between the rays and leukaemia is harder to show now that the use of X-rays is so common that few people have not been exposed at some time.

2. Carcinogenesis in the individual is a very rare event; if one assumes that there is a single critical event of carcinogenesis corresponding to each case of cancer, this happens each day to about one person in fifty thousand.

3. The lumping together of all kinds of neoplasms obscures some factors. It is as if the cause of inflammation were to be attacked considering poliomyelitis, burns, typhoid, tuberculosis and surgical wounds lumped together. There is no close similarity between the childhood neoplasms and those in the elderly, cerebral glioma and carcinoma of the rectum, strongly hereditary growths like neuroepithelioma of the retina and growths which occur so rarely that any connexion between cases is hard to conceive.

It is convenient to divide the idea of "cause" into three heads, analogous to those concerned in the discharge of a firearm: the explosion in the chamber which is the *direct cause*; the pulling of the trigger of the loaded gun, the *exciting cause* of the explosion; and the dislodging of the safety catch which may bring about the discharge of a trigger-light and loaded gun is the *predisposing cause*.

The first is parallel to what is known as the "essential" or "continuing" cause of malignant growth; it must be intra-cellular, because it has to explain the progress of transplanted or metastatic growth in which cells are alone taken to the new site. It represents a cytological change of a fundamental kind in the malignant cells, and is possibly common to many kinds of malignant cell; in this sense there may be a single cause of cancer. It must be closely bound to and not liberated from the cancer cell, since neither in transplanted growths nor in metastases of human cancer does malignant tissue induce a similar change in the host tissue.

The second or " exciting " cause is what liberated this malignant cytological change. Many substances have this action, sometimes specific for one type of cancer, sometimes producing different cancers if applied in different ways, and sometimes (e.g. 2-acetyl-amino-fluorene) when distributed through the body producing malignant changes in a dozen different organs in a series of animals. More than one substance may produce one histological kind of growth, e.g. squamous-cell carcinoma by tar or X-rays.

In these two categories there should be 100 per cent carcinogenesis from these causes (as in the gun, allowing for an occasional misfire).

The third category is not quite comparable, just as dislodging a safety catch will not inevitably lead to a discharge. Most clinical " causes " of cancer come in this group—they do not lead to cancer in every person affected, but to a percentage which varies from a negligible risk like that of a single diagnostic radiograph, to a near certainty as from the intake of highly radioactive substances into the bones. Conversely the possession of a good safety-catch may prevent cancer; parturition is known to predispose to carcinoma of the uterine cervix, which is almost unknown in nulliparae. The analogy must not be pushed too far—it is not suggested that these clinical causes of cancer work by removing protective mechanisms.

I. The Fundamental or Continuing Cause

There are grounds for hope that this may be somewhat similar throughout the whole of neoplasia, but it should be pointed out that many varieties of cancer may occur, even at one site from the malignant change in a particular cell, though how far the variation is basic and how far merely in incidental features is not known. Since the innate behaviour of the cell is determined by the nucleus mainly, and cancer may certainly be transferred to new sites by cells that contain little else than nucleus, the likely situation for the change is in the chromosomes; such change would bring about new behaviour which would be transmitted to the descendants. Support for this comes from—

1. Direct observation of abnormal mitoses in malignant cells.
2. The group of hereditary neoplasms headed by *polyposis coli* and *neuro-epithelioma retinae* in which dominant genes predestine the patient to develop these tumours without any other cause of which we are aware.
3. Comparison of the cytological changes in the chromosomes resulting from experimental exposure to X-rays and other ionizing radiations which are known to produce cancer with those resulting

from chemical carcinogens of known and relatively simple structure. Haddow has suggested that the distortion and bridging that occurs in the chromosomes from these drugs is followed by the loss of chromatin; some cells die, others evolve a new chromatin make-up with simpler enzyme methods which accounts for the de-differentiation and metabolic changes in the cancer cell.

This is the central line of research at present and if complete a single cause and cure of cancer may emerge. Up to now no difference in the biochemistry between the cancer and normal cell has emerged which is sufficient to provide a point for chemotherapeutic attack, though plenty of differences have been described.

A possible natural source of this sort of change is known in the penetrating ionizing radiation, cosmic rays, which may account for some sporadic cases of cancer; nothing can be done about that, but the danger of increasing the exposure to ionizing radiations of human manufacture becomes increasingly obvious.

II. Exciting Causes: Carcinogenesis

The search for a cause of cancer started in industrial medicine with the observations of Percival Pott (1775) on the scrotal cancer resulting in adolescence from soot-contamination incurred while sweeping chimneys naked in childhood; the observations of Dr. Joseph Bell (1876) who showed that shale-oil workers in Bathgate developed cancer from contamination of the skin, and those of Wilson (1910), then a Manchester house-surgeon, that mineral oil caused cancer in the groin area in cotton-spinners who worked with this part of their garments soaked in oil. Chemical investigation starting from these substances and animal experiments have isolated a formidable and growing list of compounds known to produce cancer when used in susceptible animals. No common morphology or molecular structure has emerged which could unify the subject and indicate possible future dangerous substances; a phenanthrene ring structure is common but not essential. Little would result from giving a long list of substances many of which are rare, or have been synthesized specially for the investigation, but some very useful lessons have already emerged—

1. The proof of the length of the incubation period and the minute quantity necessary.

2. The improbability of any infective agent. Animals in the same laboratory do not develop cancer from the experimental ones, with a single exception, the obvious infectivity of which goes far to proving that the usual cancers are not infective. This infective

growth is the *Rous sarcoma* which was found spontaneously in fowls and has proved transmissible as a virus infection to other closely related birds, but there are no similar malignant growths in mammals. Much work has been attempted to show passages of other cancers as a virus infection, but only experiments in which viable cells have been transferred show transference of growth. This includes the work of Gye with frozen cells; even his treatment was insufficient to inactivate the cells completely.

Benign growths due to filter-passing viruses are well known, and the infectivity of such was also well known long before viruses were. The school-girl knows that warts may be spread by the blood trickling from one; molluscum contagiosum was so named in 1817. In rabbits such transmitted papillomas have become malignant; but viruses extracted from the carcinoma have transmitted only the preceding papilloma.

This is entirely in keeping with the human observations on infective disease—viruses produce diseases that are conspicuously contagious; the delicacy of the viruses makes close relation likely; and though lay stories occur, hospital experience is entirely against the contagiousness of cancer. The only possible difficulty which would allow a virus origin for some cancers would be a virus with a very long incubation period. Otherwise the only role for a virus in cancer would appear to be a very subsidiary one inside the cancer cell, long resident inside it and causing cancer only when excited by some other factor: it would hardly be correct to regard such a virus as the cause of cancer.

3. CO-CARCINOGENESIS. The probability that cancer might result from the combined effect of two stimuli, unrelated to each other and at different times, and each by itself insufficient to cause malignant growth, was first raised by Berenblum (1947). He showed that sub-carcinogenic doses of certain substances known to produce cancer when applied in full doses (" initiators ") could be reinforced by a number of non-specific agents (" promoters ")—croton oil, chloroform, inflammatory exudates; Peyton Rous had previously shown that in a tar-painted ear the locations of the growths were determined to some extent by injury.

If this double causation is true of human as well as of animal cancer (it is still somewhat *sub judice*, though statistical evidence is in favour of two " events " determining each case) it might help to explain the long incubation of human cancer, waiting for the second event to happen; it certainly makes the search for a cause far more difficult; and it leaves uncertain which is to be taken as the legally responsible cause.

4. RELATION BETWEEN CARCINOGENS AND OESTROGENS. This chemical molecular relation between sterols like cholesterol, oestradiol, and known carcinogens is supported by experimental and clinical observations. Stilboestrol used to treat prostatic cancer has resulted in the development of carcinoma of the male breast, and given to hamsters has produced renal carcinoma. Substances are known which have the triple activity of oestrogenesis, carcinogenesis and action as embryonic organizers. Carcinogens can be produced from substances naturally present in the body by metabolic steps known to occur in the body; the actual substances may be needed in only microscopic quantity. In other words, there may be no need to suppose there is an external cause of cancer at all. A minor metabolic accident in steroid chemistry could so alter the cell that years later cancer might occur.

5. THE DANGER OF INDUSTRIAL CHEMICALS. Of the vast number of chemicals used in quantity in industry only a few are known to be carcinogenic. Once they are recognized as such, legislation can control the risk; this has been done with aniline and β-naphthylamine, which increase thirty times the natural risk of cancer of the urinary bladder. But neither prediction from the molecular formula nor animal experiment will safely exclude risk; man himself is virtually the only experimental animal, and the utmost caution should be used in allowing large-scale or prolonged exposure to any new substances, bearing in mind the long incubation period likely before the cancer manifests itself.

6. Practically no information is available about *benign neoplasms*; though not lethal, they are clinically important, costing much manpower and illness.

III. Predisposing Causes

A considerable number of clinical conditions are known which are more or less likely to be followed by cancer, the actual risk varying from the debatable to the near-certainty. Some of these have been alluded to already. Heavy cigarette smoking and the development of pulmonary carcinoma, Paget's osteitis deformans and bone sarcoma, leukoplakia of the oro-pharynx and vulva and squamous carcinoma, are all examples where the incidence is too high to be merely due to chance. A few examples of chronic inflammation are dangerous—bilharzial cystitis and carcinoma of the bladder; asbestosis and carcinoma of the lung; the risk of carcinoma of the gall-bladder following stones must be low, considering the frequency of gall-stones, but almost all gall-bladder cancer is associated with stones. Chronic ulceration of the skin carries a

risk that is small, because the changes are visible, the natural rate of growth slow, and the change infrequent. Chronic peptic ulceration of the stomach has been said to carry a rate of malignant change varying from 1 to 50 per cent; this is mostly based on histological points thought to indicate preceding ulceration in a cancer; the clinical observers are opposed to the view that it is of sufficient importance to take into consideration in the treatment of a case, provided it is certain that you are actually dealing with a peptic ulcer at the start. Widely differing estimates are also given for the frequency with which the nodular regeneration of a cirrhotic liver develops into carcinoma, perhaps 5 per cent being a fair average. The observations made on carcinoma of the prostate in the elderly suggest that almost every male will develop this process (though not necessarily the clinical disease) if he lives long enough: conversely carcinoma of the cervix uteri is found only in those who have borne children; nulliparae, though safe from this cancer risk, run an increased risk of carcinoma of the body of the uterus and of the breast.

IV. Older Ideas—Embryonic Rests

The undifferentiated type of rapid "embryonic" growth shown by many tumours (which is not the same thing as the rapid ordered growth of the embryo) led Cohnheim to suggest that cells lost in the normal process of development and remaining undifferentiated might spring into activity later in life and be the origin of cancers. Experimental embryology has since shown that displaced tissues though they may develop in an unusual fashion do not develop malignant tumours even in embryos, and in adults develop into implantation cysts or similar structures if they develop at all. Many developmental abnormalities are known—thyroglossal cysts, angiomatous vascular malformations, misdevelopment of complicated embryonic jig-saws like that of the face, but malignant tumours are not found in these malformations. For one benign tumour (the cysts developed from Rathke's pouch) and one malignant invasive tumour (the chordoma, derived from notochordal remnants) origin in an embryonic rest must be accepted; some teratomas probably arise in embryonic rests; but in general displacements do not naturally or essentially become tumours though tumours may arise in them.

TRAUMA is so common that scientifically it is more important as drawing attention to a tumour than causing one, but legally it is often accepted as the cause of sarcoma of bone. Patients with this disease often remember in retrospect some possibly quite minor

injury to the site, but it is almost unknown for sarcoma to develop in an injury either trivial or severe which is under treatment on its own merits.

HEREDITY, i.e. genetic alteration in the chromosomes, is a certain cause of a small number of rather rare tumours. Since few tumours antedate the reproductive period of life, there is no tendency to breed out the disease, and a small series of observations on identical twins living in widely differing surroundings has shown too great a frequency of simultaneous development of the same growth to be a coincidence. But observations in human cancer relating to the common kinds have not shown any clear line to follow in preventing the disease, though from time to time striking examples of cancer families are reported—perhaps the best being that of Napoleon Bonaparte, whose father, sister and two brothers died, as he did himself, of cancer of the stomach. Race, and even family, include other things besides genetic similarities—occupation, exposure, habits of eating and drinking—all of which have to be taken into account before regarding such incidence as due to chromosome abnormalities.

Experimentally, in mice, heredity has been shown to be very important. The susceptibility to cancer from skin painting can be segregated from the susceptibility to develop spontaneous mammary carcinoma; each cancer should therefore be considered a separate disease from the point of view of heredity; there is tenuous evidence in humans to family liability to one particular sort of cancer but not to the disease cancer as a whole. Bittner has produced a complication in mice by showing that the " heredity " is dependent on the milk suckled from the mother and not on the genes inherited from her.

Lessons from the Study of Causation

It may well appear from all this that in the individual the cause of his growth is something too brief in action, too inconspicuous, too closely interwoven in his normal life, too remote in the past to be successfully controlled, and that we are more likely to be able to cure cancer than to prevent it.

Certain steps can be taken about known carcinogens: tobacco; the indiscriminate use of X-rays both industrially and in medicine, remembering the cumulative effect of the danger; drugs of the oestrogen type and others chemically suggesting carcinogens should be used with care; the flood of new chemicals liberated on the world in industry and in drugs should be viewed with suspicion until long trial has shown them to be safe. But though some important groups

of cancer could be almost eliminated by such measures, the common gastric, colonic, mammary and uterine cancers and some less common groups such as the cerebral growths lie at present well outside our knowledge to control their causes; we have not even an entry to the problem.

Diagnosis and Control of Malignant Disease

It is essential, both for the patient and for scientific observation on the incidence and therapy of cancer, that the diagnosis should be as certain as possible. This means histological proof; only when every naked-eye diagnosis is checked by histology is it realized how often mistakes occur; to make sections only in difficult cases is not enough. Biopsy and histology are not infallible, but the material is easily preserved and can be revalued at need. Once the possibility of malignant disease in a patient has been raised, it must be proved or disproved completely, by repeating the observation if there is uncertainty. Necropsy statistics without histological backing are not reliable.

Some of the sources of fallacy in biopsy taking have been mentioned already (p. 17). The choice of tissue is largely determined by the accessibility of the part of the patient concerned; the best selection of tissue requires: (*a*) well-preserved material—avoid necrotic, sloughing or heavily inflamed areas, (*b*) a real sample of the growth or other suspected lesion. It is a common error to avoid the necrotic centre too widely and in an endeavour to provide a margin of healthy tissue for comparison to take a sample that includes only a few peripheral fragments of the lesion. Take the largest sample possible; it costs no more to cut and stain a large section than a small one. In selecting a lymph-node, the largest available is much more valuable than a small peripheral node, which may show only very early slight changes making for difficulty in diagnosis; but other things being equal avoid upper cervical (tonsillar) and inguinal glands, for they are more likely to be distorted by post-inflammatory fibrosis. If more than one piece of tissue can be obtained without hardship to the patient, the probability of reaching the correct diagnosis is increased: the advantages of aspiration or "needle" biopsy, and of exfoliative cytology, lie in the case with which they can be repeated.

In the histological study of such material, there may be insufficient depth of tissue to show invasion, the surgeon being able to produce only a superficial shaving of the growth; again, the growth in the part removed may be in a pre-invasive state. Great emphasis must then be placed on atypicality: the size and regularity of the nuclei

compared with normal tissues of the area; but it will often be a matter of opinion, and the ease with which paraffin blocks can be sent for opinion, to other pathologists should be remembered. (It is much better to send them than a fragile single stained slide; and it is important to send as much clinical information and naked-eye appearances as possible.) The temptation is to over-diagnose; missing an early cancer is much less likely to be forgiven than causing an unnecessary operation. But your opinion must be given on the material you survey and not on probabilities; these are matters for the clinician; if you can firmly diagnose cancer, he can act in confidence; if your report is doubtful or negative, it relates only to a small piece of tissue, and he must reconsider the clinical picture and possibly repeat the biopsy if clinically desirable. It is permissible to point this out to him, and it is well to have an arrangement for reviewing the material together if clinical and pathological diagnosis do not tally, and to check the identity of the specimen examined with that removed from the patient.

Control

Once the diagnosis is firm, the entire malignant area must be destroyed. In the present state of our knowledge no other possibility exists of controlling the disease; the methods available are surgery and irradiation. Surgery may be undesirable for many reasons, but if available it is the only way in which the growth can be removed without damage to any healthy tissue, beyond acute aseptic inflammation in a limited area. Destruction nearly as complete can be achieved by radiotherapy, but not without damage to adjacent tissues or to overlying skin, damage that is wider and less easily repaired than the trauma of surgery. The area of this damage can be limited greatly by technique, and some growths—notably those of squamous epithelium, and the lymphoid tissue—can be controlled by doses which do little harm to other tissues. On the other hand, some other growths, e.g. fibrosarcoma, mucus-secreting carcinoma, are extremely resistant. Even when extensive metastasis renders cure out of the question, radiation may alleviate local pain and such symptoms as mediastinal obstruction. It is however rarely completely curative, and is not without disadvantages of its own in irradiation reactions.

Four lines of medical treatment are being opened up. The treatment of hormone-dependent growths by opposing hormones has already been alluded to in the treatment of carcinoma of the breast and prostate. Substances which interfere with the mitosis of cells (urethane, colchicine) have been tried, in the hope that they will

check the growth of the tumours. The synthesis of nucleic acid is opposed by folic-acid antagonists, and many pterins have been used. A fourth group of cytotoxic substances, such as the nitrogen mustards and myleran, have found limited application as direct lethal agents on some malignant cells. These are being explored, but at present hold only slight hope of temporary amelioration; they may modify but do not strike at the root of malignant behaviour; they are not specific enough, and their actions overflow on to healthy tissues.

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CHAPTER 8

DISORDERS ASSOCIATED WITH REPRODUCTION

THOUGH the overall efficiency of this process is proved by the continuance of the human race, there is much abnormal, which can be considered under four headings—

1. Abnormalities in the mother resulting from prëgnancy and labour.
2. Abnormalities in the foetus resulting from intra-uterine defects.
3. Abnormalities in the foetus resulting from abnormal inherited chromatin derived from one or other parent.
4. Foetal abnormalities associated with birth.

Maternal Abnormalities Connected with Pregnancy and Labour

The physiological strain of the pregnancy on the nutrition and general health of the mother may not cause much disability if she is in perfect health, but it will accentuate any pre-existing disease or deficiency. The blood-volume is increased by about a quarter, which is a considerable additional burden on the heart, and patients with heart failure are likely to be made worse. Similar deterioration may occur with several other diseases, tuberculosis, nephritis and disseminated sclerosis being examples, but detailed consideration of these problems is outside the scope of the book.

Toxic material from the foetus and placenta can reach the maternal circulation. The proof of the permeability of the placental barrier is that antigens in the foetus may cause antibody formation in the mother, an event of no immediate importance to her, but in the special case of the Rh-antigens having dangers to the present and future pregnancies, and to future transfusions in the mother.

The best examples of toxic absorption come from an uncertain source, possibly the placenta; separation of this organ is accompanied by the formation of a retro-placental haematoma, and death of part of the placenta. Toxins derived from the digestion and absorption of these, and other substances related to the pregnancy, can have serious pressor effects on the circulation of the mother,

and on the function of liver and kidneys. These collectively are known as the *toxaemias of pregnancy*. The life of the foetus is in great danger if indeed the damage to its essential placenta has not killed it, and the mother may die; but if the contents of the uterus are discharged the changes are reversible, provided the patient does not die from acute tubular necrosis in the kidney (p. 190).

Associated with parturition, or with the abortion of foetuses that have died, are the dangers of *haemorrhage*, particularly when the very vascular placenta is in the lower part of the uterus, so that it has to be torn away from the uterus before the baby can be born, that too in a part of the uterus where contraction of the uterine muscle cannot occlude the venous sinuses quickly after the birth; *infection* of the placental site (puerperal sepsis) with streptococci, *Clostridia*, or other organisms; air embolism (p. 131); and *rupture* of the uterine wall if its muscle acts when foetal or pelvic malformation prevent normal delivery. These pathological processes are merely special cases of events seen elsewhere in pathology.

Peculiar to the pregnant woman is a very rare placental tumour, *chorion–carcinoma*. This may follow a normal pregnancy, but the majority follow a foetal abnormality known as *hydatidiform mole*. The reason for these two malformations of the placenta is unknown, but they are diseases of the placenta and not of the mother, and do not recur in succeeding pregnancies. In the hydatidiform mole, the normal vascularization of the trophoblastic villi does not occur; the embryo therefore dies, but the placenta may grow for several weeks into a mass of vesicles compared to a heap of white currants, these being formed of swollen mucoid villi. In the majority of cases, this aborts and there is no further trouble; in a very small number of cases, and occasionally following abortion or even a normal pregnancy, the trophoblast goes on growing and invading the uterine muscle, with haemorrhage and necrosis, and a tendency to metastasize by the blood-stream. In this invasiveness, the trophoblast is merely exaggerating its usual function of eroding the decidua and maternal blood-vessels to secure the nutrition of the embryo; its physiological normality is shown by the elaboration of placental gonadotropic hormone by both the mole and the chorion–carcinoma in unusual amounts; this helps in diagnosis and follow-up after removal of what may be a rapidly fatal growth.

ECTOPIC GESTATION is a further way in which the foetus may harm the mother. Fertilization normally occurs in the Fallopian tube, but implantation may also occur there if the movements of the blastocyst are delayed, for example by old inflammatory fibrosis in the tube. The placenta then develops in the thin wall of the tube.

Though rarely such pregnancies may go to term, the usual fate is rupture of the tubal wall or discharge of the embryo through the fimbrial end of the tube, with very severe intra-abdominal bleeding from the placental site.

Intra-uterine Defects in Foetal Nutrition

During nine months' intra-uterine life, the foetus is nourished by its placenta, an organ with considerable selective powers of transmission with the whole efficiency of the maternal organism behind it to protect it from infection and intoxication. This stage of life is therefore well sheltered from certain causes of ill-health, and defects arising during it were assigned, perhaps too easily, to genetic causes.

PLACENTATION. The implantation of the blastocyst is controlled by progesterone derived from the corpus luteum (and it in turn by the luteotrophin of the adenohypophysis). There is a brief period before the trophoblast itself secretes chorionic gonadotropic hormones which maintain the corpus luteum. Although occasional cases of repeated early abortion have been successfully treated by progesterone, nothing is really known about the frequency with which implantation goes wrong or the causes of this.

TRANSMISSION OF MATERNAL INFECTION through the placenta is uncommon apart from *congenital syphilis*. If syphilis in the mother is active, the result is abortion; as maternal infection dies out, less severe foetal infection results in the birth of children with syphilitic hepatitis and diffuse spirochaetal lesions of the skin and bones; later still, children are born who show no evidence of the disease until they reach late childhood, when dental and bony abnormalities and central nervous disease may be seen. Treatment of syphilis has now made this a very rare disease.

Of other infections, tuberculosis will occasionally pass the placental barrier, and brucellosis may involve the placenta and amniotic sac and cause abortion; the only neoplasm which will pass is the malignant melanoma; the leukaemias do not.

It has become clear lately that in the early stages of intra-uterine life maternal infections may have an effect on the developing embryo. The association between maternal rubella, congenital cataracts and congenital heart maldevelopments was shown by Gregg and Swann in 1941; this happens only in the first two months of pregnancy, after which the developing embryo is no longer affected by the virus. This is as yet the only proven case, but many important foetal abnormalities appear (from the timing of the normal development of the affected parts) to be occurring at about the second month (e.g. mongolism) and may be due to maternal

infection or toxins in the widest sense. In the later stages, unless a poison or infection actually kills the foetus no disturbance of its development has been proved as a consequence. Mongolism, a common important cause of mental defect, is strongly correlated with age of the mother and is therefore likely to be due to maternal environment or to faulty chromatin in the ovum.

In a small number of pregnancies the placenta appears permeable to antigens and antibodies; the foetus, inheriting genetically blood groups different from the mother's, may pass these red-cell antigens into her circulation. When the maternal antibodies find their way back into the foetus, haemolysis of the foetal red cells may occur with fatal anaemia, usually just after the baby is born. This process is known as erythroblastosis foetalis (from the appearance of immature red cells in the infant's blood); the most severe examples may lead to death *in utero* with great oedema of the foetus (hydrops foetalis) or to intense jaundice shortly after birth (icterus gravis), far more marked than the physiological breakdown of excess haemoglobin which occurs normally. The antigens concerned belong to the Rh-system, and occur when a Rh-negative mother is immunized by her unborn Rh-positive child; but placental transmission does not occur in every pregnancy of this type.

The placenta, which is a very efficient organ to begin with, becomes less so in later pregnancy, both because of the increasing size of the foetus and its own degenerations: these include the coating of the villi with fibrin, the clotting of the blood on the maternal side (infarcts of the placenta), and the formation of retro-placental blood clot. The foetus may become seriously anoxic as a result and die. Extremely little is known about the physiology of the human placenta, and not much more about animal placentae. Its importance as a foetal organ is neglected, but no pathological examination of a dead new-born baby is complete without it.

Genetic Disease in the Foetus

The inheritance of features, which are either anatomical structural facts or physiologically innocuous, has been worked out along lines started by Mendel in 1865, largely using controlled breeding in animals, which have a generation time that allows the investigator to survey much material quickly. The inheritance of human disease cannot be so studied, because the disease interferes with the reproduction of the sufferer, human breeding cannot be controlled or ordered, and observation of the results of uncontrolled breeding is hampered by the few generations that an individual can observe; he is forced back on records of past generations of uncertain

accuracy. Moreover, as our knowledge of genetics from animal sources and the medical accuracy of our observations have improved, the reproductive rate of most civilized countries has dropped, which further increases the difficulty of detecting genetic events.

In general, the sufferer must breed before it is easy to prove that a disease is genetic in origin; familial incidence is suggestive, since it is unlikely that adverse influences of other sorts would affect a series of pregnancies, but it is not conclusive. It will thus be difficult to prove a genetic origin for disorders which prove fatal in young people, and even more so when the disease is fatal *in utero*: unless extended family histories are available, as they are for a few uncommon but striking defects, which show a characteristic pattern of Mendelian inheritance, or unless there is linkage to features which can be proved to be hereditary. The full examination of most early abortions and the collection of their family histories has not yet been carried out, so that the position is quite obscure.

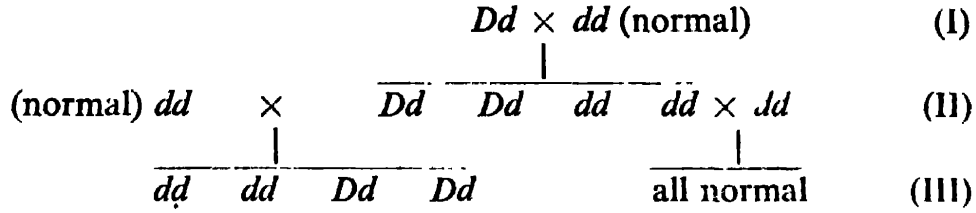
Where the inherited feature is physiological, such as the antigens of the red blood-corpuscle, or when it is of little clinical handicap, such as many defects in the skin and its appendages, the pattern of inheritance is well worked out. The association of certain blood groups with certain diseases, a study which has already had suggestive results, may indicate that the mucopolysaccharides determining the blood groups also affect the physiological response of the body to disease which at present is not clearly or closely related to the genetic background. No surprise is shown if a child resembles its parent in features, and it is equally likely that anatomical resemblance exists in parts of the body less exposed to examination; similarly physiological resemblances in function may be seen, perhaps most conspicuously in some allergic responses.

Proof of inheritance of a character will depend on whether the gene determining it is dominant, or whether it is a recessive allelomorph.

DOMINANT INHERITANCE. Here all carriers of the gene suffer from the disease. Unless like that of Huntington's chorea, in which the gene does not produce its effect till long after reproductive life, serious genetic defects will obliterate themselves in a generation; even the less serious ones tend to do so in human communities, from eugenic considerations. The presence of such lethal genes in a human pedigree must largely depend on spontaneous mutation. Hereditary polyposis of the colon, leading to cancer, is an example of dominant inheritance; less serious dominant genetic effects are well known, von Recklinghausen's neurofibromatosis and certain deformities of bones providing some of the best-known and easiest

to follow. The pattern of inheritance is determined by the following factors.

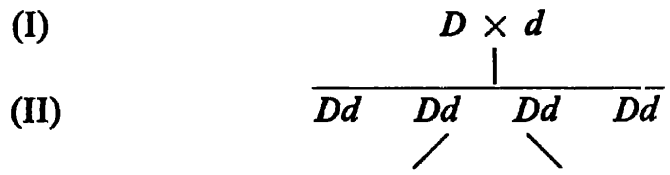
The sufferer from a disease determined by a dominant gene is usually heterozygous; the homozygous state could only result from two carriers marrying, and since they both show the defect this is less likely. The results of marriage of such people can be represented (*D* the dominant gene, *d* its recessive normal allelomorph)—



that is half the progeny will be heterozygous showing the defect; half will be normal, neither carrying nor showing. The gene will persist through many generations in a visible form, but will never be latent. It is to be observed that with the present small families the chance of all the children being *dd* and the gene dying out is considerable. The characteristic features, then, of dominant inheritance are that the defect appears in about half the children through every one of many generations; some have been traced back 400 years; children who do not show the defect are perfectly safe to marry. When a condition shows itself in grandparent, parent and child, it is safe to assume that it is genetic, and due to a dominant gene.

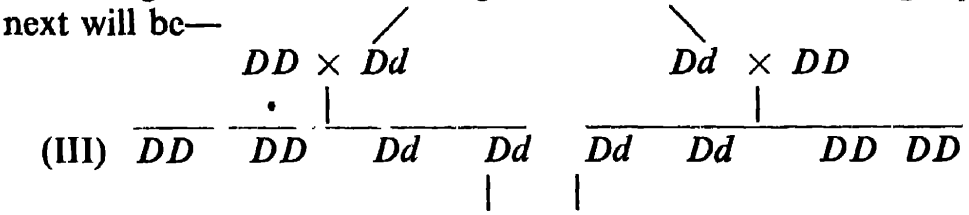
RECESSIVE INHERITANCE. Here a carrier state is very important, where a person inheriting the dominant allelomorph from one parent and the recessive from the other will not show the disease, but will hand it on in his chromosomes to the next generation; only those who inherit the recessive factor from both parents will show the defect. As an example the biochemical abnormality phenylpyruvic dementia can be quoted.

If the pedigree is considered in which a mutation results in the appearance of a recessive allelomorph *d* for the normal dominant *D*, the progeny, receiving *d* from one parent and *D* from the other normal parent, will all have the genotype *Dd*—

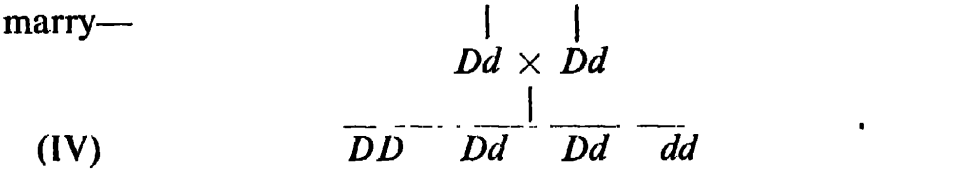


These will be carriers, but the dominant *D* will prevent them

exhibiting the disease. If this generation marries normal people the next will be—



Normal marrying carrier, results in normals and carriers in equal numbers. The normal individuals play no further part in the transmission; the carriers are indistinguishable externally. If they marry—



Carrier marriage, results in one wholly normal, two apparently normal, but carrying the recessive gene, and one sufferer with the recessive gene alone.

Note that since half the cousins in the previous generation (III) were *DD*, half *Dd*, cousin marriages will in a quarter of the cases be carrier marriages.

Since it is more probable that parents carrying a recessive gene will owe it to a common ancestor than to random mutation, marriage between blood relations is the commonest source of the defects of this kind. Abnormalities seen in the progeny of cousins suggest that they may have genetic causes; but since only one in four cousin marriages is a carrier marriage, and only one in four children of a carrier marriage is a homozygous recessive, the actual risk of a particular recessive gene becoming manifest is only 1 to 15. There may, however, be more than one recessive gene latent, which are inherited independently. Although the risks of defect from inbreeding are great and so stressed, the ancestors and descendants of Charles Darwin provide a striking example of inbred intellectual vigour.

The lapse of time before the defect becomes manifest is notable—the third generation, about fifty years after the origin of the defective gene in human heredity.

If the recessive sufferers marry, the outcome will depend on the partner: (*a*) normal, all children will be carriers; (*b*) a carrier, half carriers, half recessive homozygous sufferers; (*c*) another recessive, all the children will be recessive.

With carriers, as long as fresh blood is being brought in, there is no chance of the gene becoming manifest; on the other hand, the

gene will persist indefinitely unless it is eliminated by linkage with disadvantages or by the operations of chance. With small families, chance is becoming very important; the Mendelian ratios may be altered widely; much mathematical calculation is necessary to assess the fit of observations with the theoretical ratios.

Note too that there are far more carriers than recessives, even in the above pedigrees. If interbreeding of relatives is excluded, calculation based on theories of probability shows that, if a recessive turns up once in a million individuals, there must be about 2,000 carriers in that million. Eugenic control of recessives showing the defect will therefore have a negligible influence on the abundance of recessive genes in the carriers indistinguishable among the normal population.

Spontaneous mutation of normal genes, possibly resulting from natural ionizing radiation and certainly increased by ionizing radiation in experimental animals, is a constant source of new characters, not necessarily disadvantageous though usually so. The natural frequency of this event can be calculated for lethal or disadvantageous genes, when the frequency of their effects in the whole population is known. Mutation by irradiation commonly results in recessive genes: the delay before the results of irradiation will appear should be noted.

SEX-LINKED INHERITANCE. Of the twenty-three pairs of chromosomes now recognized at the reduction division in the formation of the gametes, twenty-two are pairs of like chromosomes, known as the autosomes. The other pair, the sex chromosomes, are alike in the female, called "*X*-chromosomes," but in the male the pair is made up of a single *X*- and a *Y*-chromosome which appears to carry few genes. (Excess chromatin (possibly related to the *XX*-chromosomes) may be recognized as a dot on the nuclear membrane of cells in the female body, conveniently on desquamated oral mucosal cells or polymorph leucocytes.) The fertilization of the *X*-chromosome in the ovum by either an *X*- or *Y*-chromosome in the sperm determines the sex of the zygote. The *X*- and *Y*-sperm are not at present distinguishable, but if they became separable sex control of the offspring would be possible. They should theoretically be present in equal numbers but there is a slight excess of male births and more of male premature stillbirths; whether the ratio at fertilization is equal and the inequality is due to adverse influences of the *XX* condition very early *in utero*, or whether the *Y*-sperm is favoured in the probability of fertilization is likewise unknown at present.

As well as determining sexuality, some genes for physical and chemical features are located on the *X*-chromosome. These may be

dominant or recessive, and are inherited in the usual way; but with recessive characters (x), the dominant normal X will prevent them showing in the heterozygous female (Xx), whereas the male (xY) with only one x chromosome and no protection from the cypher Y will show the recessive traits.

The best-known example is the disease haemophilia in which a globulin necessary for clotting (see p. 126) is absent from the patient's blood. This arises as a *relatively* frequent mutation in the population, so keeping alive a gene which is the cause of a disease so serious and so clearly hereditary that the gene would rapidly die out as a result of natural and eugenic considerations in human society. If such x gametes are fertilized by a normal man, the results will be either—

xX: normal X from father dominant, a female carrier
xY: normal Y from father insignificant, a male sufferer

If the carriers (xX) marry normal (XY) men, the results will be (female gamete first)

XY normal male
xY affected male
XX normal female
xX carrier female

i.e. half the sons suffer, half the daughters carry.

If an affected man has children in spite of his disease, the result will be, if he marries a normal woman,

$$XX \times xY$$

$$Xx \quad Xx \quad XY \quad XY$$

i.e. all his daughters carry, but his sons are normal. If in the next generation (normal)

$$XY \times Xx$$

(progeny of sons normal and can be ignored)

$$Xx \quad XX$$

we assume no male child is born then in the great-grand-children we have

$$XY \times Xx$$

$$xY \quad \ldots\ldots$$

the appearance of a haemophiliac who is likely to be considered a fresh mutation, unless an unusually good family history is available about the grandparent of the mother. If the

appearance of the disease is postponed still further by the birth of girls only (half of whom will be carriers) elucidation is even more difficult. The rarest happening is the marriage of an affected male with a carrier female:

$$Xx \times xY$$

$$Xx \quad xx \quad xY \quad XY$$

giving female carrier, female sufferer, affected male and normal male in equal numbers.

This theoretical position has rarely been realized in haemophilia because of the usual early death or invalidism of the affected males and a possible lethal effect on the *xx in utero*; but with a defect less dangerous or conspicuous than haemophilia transmission could clearly continue indefinitely.

This discussion has not taken into account the inheritance that depends on simultaneous action of more than one gene, and dominant and recessive have been used as if they were absolute characters, whereas partial dominance in the heterozygote is well known. There is only room here to explore the fringe of the whole subject.

Mechanism of Gene Action

The gene must be related to the nucleo-protein molecules which compose the chromatin of the nucleus, but no certain estimate of its size has been made. Models have been designed which can theoretically reproduce the two actions of a gene—that of replicating itself for the next generation and of modifying some bodily activity, probably enzymically; Haldane has said " one gene—one enzyme." The fact that one gene apparently controls many different events may be explained by these events in turn being dependent on some single chemical reaction not yet elucidated. In other cases—" multifactorial inheritance "—one event may be determined by the combined action of many such genetic units. The presence of these units is inferred from physiological events taking place in the growth of the intact animal.

The congenital conspicuous abnormalities that are studied by geneticists make up a really very insignificant part of our inheritance. The layman's observation that parent and child are alike relates in the main not to the presence or absence of a single peculiarity but to the local pattern of intensity of growth in the quantity of tissue making up the face. If we accept that the face is not the only part

of the body whose growth is controlled in this way, and that laymen are also right when they recognize that a child may inherit its parents' temper as well as looks, there is clearly a wide field in which minor variations in the intensity of genetic effects may relate to human illness, and indeed determine whether a patient falls ill or not; a slight increase in the speed of antibody formation, versus the steady speed of growth of a germ, could result in immunity.

The relation of these common important quantitative variations that result from inherited chromatin is obscure; but in one special case, sickle-cell anaemia, we know more. It has been shown that in the haemoglobin whose abnormality causes the disease (p. 176) there is one single amino-acid different in the 300 or so that make up the normal globin part of the haemoglobin molecule; this abnormality in the building-up of the molecule is the effect of the presence of the gene. If the gene is present from both parents (homozygous) the abnormality is so severe that it proves fatal from haemolytic anaemia; if however the gene is heterozygous, it actually confers an advantage on its owner in that he is unusually resistant to the endemic malignant tertian malaria; this compensation keeps the gene alive in the population. Now that we know the mechanism, the state of affairs can be explained; otherwise it would appear that there was an association between the gene for sickle-cell anaemia and that for an immunity to malaria. Some apparent linkages may be due to this kind of double action.

It is striking how rarely the ground-plan of the development of the body goes wrong, even allowing for the early stage at which gross defects would prove non-viable. The commonest example is provided by defects in the formation of the spinal cord and brain due to improper gastrula formation, which are seen in the new-born child as anencephaly and the various grades of spina bifida. This may be due to abnormal intra-uterine environment and so be developmental rather than genetic, but certain non-formations of the distal parts of the limbs are hereditary congenital abnormalities.

Familial Disease

There are many examples in pathology where serious disease involves many members of a family, but the affected individuals do not survive to breed. The assumption that these are genetic in origin is likely, for consanguinity is commoner in the parents than in the population in general, and the defects are so local and specialized that it is easier to conceive them as the action of a gene than as the results of any environmental influence. Genetics and environment may be combined; erythroblastosis foetalis (p. 261) is basically

genetic depending on blood-group inheritance, but in fact is expressed only in that small proportion of Rh-positive pregnancies in Rh-negative mothers in which a placental (environmental) factor permits the passage of antigens and antibodies.

Some of the best examples of genetic disease fall under the heading of congenital abnormalities of metabolism. Many are known, all are rare, most are serious and quickly fatal. Concentration of the abnormality on the metabolism of a single substance in all relevant cells throughout the body is suggestive of the absence of a critical enzyme, a pattern that fits what is known of the action of genes and is very unlike any environmental factor. Most of the conditions are familial, which is presumptive evidence of genetic origin.

Such are xanthomatosis (Hand–Schuller–Christian disease), in which cholesterol metabolism is affected, Tay–Sachs disease (phospholipin accumulation in retinal ganglion cells and in neurones), van Gierke's disease (glycogen is stored in liver and heart but cannot be broken down) and Gaucher's disease (sphingomyelin storage in reticulum cells of spleen and marrow); all are associated with deficient action of the cells concerned, and neighbouring cells may be affected by pressure or other indirect effects. The diseases are at present untreatable, since restoration of normal cellular function is impossible when the defect is in the basic material of the cell. The diseases are so rare that details must be found in larger books; they are so serious that the sufferers rarely breed.

A more benign group, not really uncommon, has been brought into the light by biochemical examination of the urine; metabolic abnormalities in the handling of many amino-acids and galactose are known.

Disorders Acquired at Birth

At birth, three things happen more or less together: the foetus is violently compressed and squeezed through a narrow passage, during which process the contractions of the uterus shut off the placental circulation; the cardio-vascular system instead of supplying functionless lungs and an extremely large and active special organ in the placenta has to change over to the adult pattern of circulation; and the lungs have to be expanded and the nervous control of respiration begin. All three are sources of disease.

Birth injuries affect principally the skull and its contents. Moulding of the pliable bones is usual and if severe may be associated with tearing of the intra-cranial veins and haemorrhage or thrombosis; brain damage so caused is the reason for some forms of congenital

defect of mind or paralysis. These injuries are more frequent if the birth is unduly prolonged or unduly precipitate, or if the position of the foetus at birth (presentation) is wrong. Cerebral anoxia may be as significant as more obvious trauma.

At birth, the ductus arteriosus and the foramen ovale should close, separating the pulmonary and the systemic circulation; patency of both may persist, the foramen usually only as a slit of no importance, but the ductus acting as a significant arterio–venous leak. Reasons for this failure to close are not known. The other foetal vessels concerned with the placental circulation are occluded by thrombus within a few days of birth, but the ductus is closed by the action of the muscle in its wall.

The establishment of respiration is more complex, since it requires not only patent air passages but also intact medullary centres; cerebral injury may affect them, as may a premature birth when they are not ready to function. The air passages during foetal life become filled with amniotic fluid, and material derived from this fluid, which contains desquamated cells from the skin and other matter, may be found inhaled into the alveoli and hinder their expansion. Full expansion of the lungs may take several days of normal respiration; weakness of the respiratory movements as well as material plugging the bronchi leads to collapse, anoxia and infection.

The high haemoglobin concentration necessary for the anoxia of the last weeks of foetal life is no longer required and is broken down during the first week of life with the development of a moderate degree of physiological jaundice. Exchange of foetal for adult haemoglobin takes place more slowly. Vitamin K may be lacking in the mother; since the baby will not make its own until its alimentary tract is contaminated with the appropriate micro-organisms, there may be a brief period of deficiency leading to haemorrhagic disease in the newly born.

Malformations of the air passages and bowel, which were of no significance when life was maintained by the placenta, become important, and failure to develop a lumen in the oesophagus, bile-duct or intestine (usually in the duodenum or at the anus) will now show up; these must have happened long before, but the cause of this defect is unknown.

With the end of the neonatal period about one month after birth these changes will be mostly over, and the infant ready to face the other perils to its life described from page 5 onwards.

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